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ETHNOMEDICAL, BOTANICAL AND PHYTOCHEMICAL ASPECTS OF NATURAL HALLUCINOGENS

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ABSTRACT

More than 200 species and/or varieties of higher plants, as well as numerous species of basidiomycetes, are reported in the literature to have been used for their hallucinatory and/or euphoriant effects. Due to a paucity of research, only a few of these have been confirmed as definitely hallucinogenic in man or animals. This article reviews all of those plants now known to have a scientific basis for producing hallucinogenic effects in man or for which reliable ethnobotanical data are available to indicate that they could be hallucinogenic. Those plants alleged to be hallucinatory, but where substantive proof of this effect may be lacking, are summarily included for completeness and in the hope of stimulating investigation.

The hallucinogens of higher plant origin alone are found in 146 genera in more than 50 families. In virtually every instance in which the active constituents are known, their chemical skeletons are unique to a specific genus or to a very closely related genus.

It is interesting to note that of more than 200 species of hallucinogenic plants only two are legally prohibited from use in the United States by Federal law: *Cannabis sativa* and *Tabernanthe Iboga*. Two or three others are illegal in a few states.

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INTRODUCTION

Many reviews covering the broad subject of hallucinogenic plants have been published in recent years (Agurell 1969; Brown 1972; Der Marderosian 1966, 1967a, 1967b; Emboden, Jr., 1972, 1979; Farnsworth 1968, 1969; Furst 1972; Heim 1963b; Heim et al. 1967; Hoffer and Osmund 1967; Holmstedt and Kline 1967; Ott 1976a; Pelt 1971; Schultes 1961a and b, 1963, 1965, 1966a, 1969a, b, c, and d, 1970a, b, c, and d, 1972a and b, 1976a, b, and c, 1981; Schultes and Hofmann 1973, 1979, 1980; Stafford 1977; Wagner 1969). In addition, many reviews on various aspects of *Cannabis* and the cannabinoids have recently appeared (Abel 1976; Bailey 1974; Bech et al. 1974; Bhargava 1978; Bloch et al. 1978; Braude and Szara 1976a, 1976b; Carr et al. 1970; Goode 1970; Graham 1976; Grinspoon 1971; Hanus and Krejci 1974; Joyce and Curry 1970; Kurzman and Fullerton 1975; Lemberger and Rubin 1975; Lewis 1972; Mechoulam 1970, 1973; Mechoulam et al. 1976; Mendelson et al. 1974; Merlin 1972; Miller and Drew 1974; Morris and Farnsworth 1973; Nahas 1976; Neumeyer and Shagoury 1971; Pagel and Sanders 1976; Paxton and Crown 1970; Quimby 1974; Razdan 1973; Rubin 1975; Rubin and Comitas 1975; Saulle 1973; Schönhofea 1973; Schultes 1973; Schultes et al. 1974; Small 1976; Small and Cronquist 1976; Small 1979; Stefanis, Dornbush and Fink 1977; Turner at al. 1980; and Waller et al. 1976). The chemistry, synthesis and pharmacology of these cannabinoids have been of major concern in most of the foregoing reviews. Although the current literature of hallucinogens is voluminous (for example from 300 to 400 original research papers are being published annually on various aspects of *Cannabis* alone), our fundamental knowledge in the field of these drugs has probably not increased in proportion to the amount of research in progress.

From the vast array of species in the Plant Kingdom—variously estimated at from 200,000 to 800,000—a few have been employed in primitive societies for millennia to induce visual, auditory, tactile, and other hallucinations. Because of their unearthly effects that often defy description, they have usually been considered sacred and have played central roles as sacra-

ments in aboriginal religions (Schultes 1969a; Schultes and Hofmann, 1979).

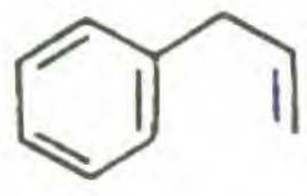
Scientific interest in hallucinogenic agents remains high in the hope of finding potentially valuable drugs for use in experimental or even therapeutic psychiatry and also because they might prove useful as tools to study biochemical origins of mental abnormalities.

While psychoactive species are widely scattered throughout the plant world, they appear to be more or less concentrated amongst the fungi and the angiosperms. The bacteria, algae, lichens, bryophytes, ferns and gymnosperms seem to be notably poor or lacking in species with hallucinogenic properties (Schultes 1969c, 1969d, 1970a, 1981; Schultes and Hofmann 1980). These hallucinogenic properties can be ascribed, likewise, to only a few kinds of organic constituents, which may be conveniently divided into two broad groups: nitrogenous and non-nitrogenous compounds (Der Marderosian 1967a; Farnsworth 1968, 1969; Schultes 1970c; Schultes and Hofmann 1973 and 1980). See Figure 1 for the basic chemical skeletons of these compounds.

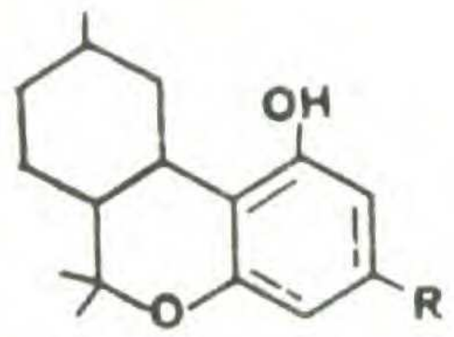
The nitrogenous compounds play by far the greater role and comprise, for the most part, alkaloids or related substances, the majority of which are or may be biogenetically derived from the indolic amino acid tryptophan. They may be classified into the following groups: 1. β-carbolines; 2. ergolines; 3. indoles; 4. isoxazoles; 5. β-phenylethylamines; 6. quinolizidines; 7. tropanes; and 8. tryptamines. Non-nitrogenous compounds, which are the active principles in at least two well known hallucinogens, include monoterpenoid chromenes and phenylpropenes.

In the study of hallucinogenic plants, two considerations must be borne in mind. One consideration reminds us that, although some of these psychoactive plants are used in primitive societies, their active chemical principles are as yet not known. The other emphasizes that man undoubtedly has utilized only a few of the species that actually do possess hallucinogenic principles. We are, as yet, far from knowing how many plants are endowed with psychotomimetic constituents, but there are certainly many more than the few purposefully employed by man as hallucinogens.

NON-NITROGENOUS HALLUCINOGENS

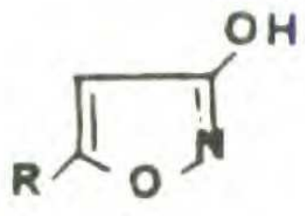


Phenylpropenes

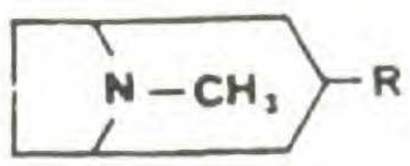


Monoterpenoid Chromenes
(Cannabinoids)

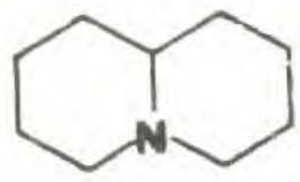
NITROGENOUS HALLUCINOGENS



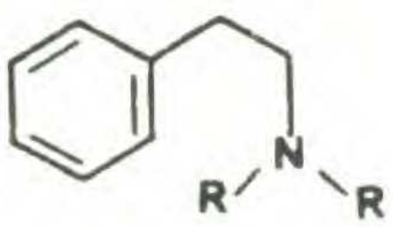
Isoxazoles



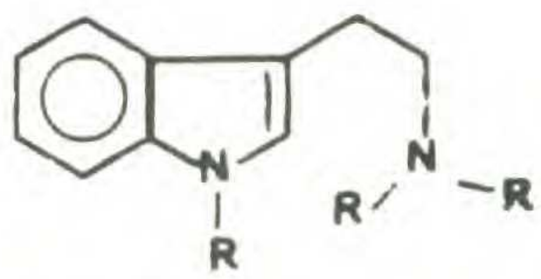
Tropanes



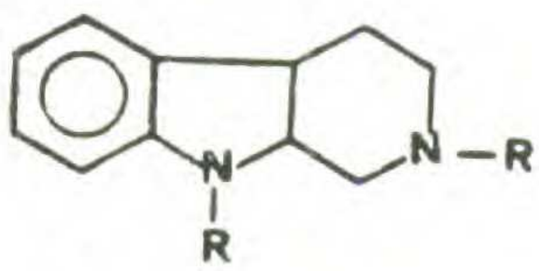
Quinolizidines



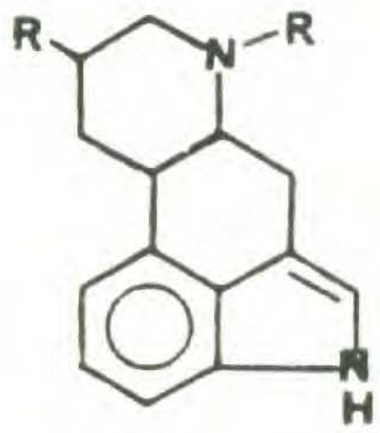
β-Phenethylamines



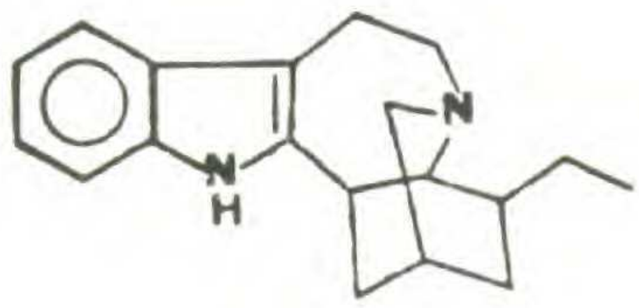
Tryptamines



β-Carbolines



Ergolines



Iboga Indoles

Figure 1. Basic skeleta of principal hallucinogens

While almost all hallucinogenic compounds are of vegetal origin, a few may be wholly or partly synthetic. The potent hallucinogen, lysergic acid diethylamide (LSD), although very closely allied chemically to the naturally occurring ergolines, has not been found in the Plant Kingdom.

NON-NITROGENOUS PRINCIPLES

1. Monoterpenoid Chromenes

Cannabaceae

Cannabis L.

The most important of the non-nitrogenous hallucinogens are the monoterpenoid chromenes, such as those found in, and apparently restricted to, the genus *Cannabis*. Products used as hallucinogens from this genus are known as *marihuana, hashish, bhang, ganja,* etc.

Various aspects of *Cannabis* have been authoritatively reviewed in recent years, including the botany, chemistry, pharmacology, synthesis of active and inactive cannabinoids, metabolism in man and animals, etc. (Abel 1976; Anderson 1974; Bailey 1974; Bech et al. 1974; Bhargava 1978; Bloch et al. 1978; Braude and Szara 1976a and b; Carr et al. 1970; Clark and del Giudice 1978; Graham 1976; Hanus and Krejci 1974; Iversen, Iversen and Snyder 1978; Iversen, Iversen and Snyder 1978; Joyce and Curry 1970; Clark and del Giudice 1978; Graham 1976; Lemberger and Rubin 1975; Lewis 1972; Mechoulam 1970, 1973; Mechoulam et al. 1976; Mendelson et al. 1974; Miller and Drew 1974; Morris and Farnsworth 1973; Neumeyer and Shagoury 1971; Paxton and Crown 1972; Quimby 1974; Razdan 1973; Salemink 1978; Salzman 1979; Saulle 1973; Schonhofea 1973; Schultes 1973; Schultes et al. 1974; Small 1976 and 1979; Small and Cronquist 1976; Stueck 1979; and Turner et al. 1980). Of special interest is a recent annotated bibliography on marihuana, covering all periodical references appearing in the scientific literature from 1964 through 1974 (Waller et al. 1976).

Since more has been published on *Cannabis* and its constituents than on any other natural hallucinogen, this section must be treated in greater detail than others.

a. THE FORENSIC-TAXONOMIC DISPUTE. Only during the past seven or eight years has the importance of the monotypic *vs.* polytypic status of *Cannabis* demanded popular attention. The reason has its roots in legal arguments, especially in the United States. These arguments hinge on the question of whether forensic material of *Cannabis* can be identified as coming from *C. sativa* L., when the possibility of the existence of other species is real, if not actual (Anderson 1974; Emboden 1974; Schultes et al. 1974). In most states and in several countries, the law defines marihuana as a product only of *C. sativa.* If more than one species exists, legal authorities must prove by identification that suspect material contains *C. sativa* and is not actually any of the other species (Fullerton and Kurzman 1974).

Since the usual methods for establishing the identity of a marihuana sample include (a) microscopy, (b) a colour test, such as the Duquenois-Levine test and (c) some type of chromatographic evidence, i.e. thin-layer chromatography, gas-liquid-chromatography, etc., one must have a knowledge of the results that would be obtained with these analyses using authenticated specimens of all acknowledged species of *Cannabis;* otherwise, the presence of *C. sativa* cannot be legally proved. It should also be borne in mind that when, as is usually the case with most legally confiscated samples of *Cannabis,* most if not all diagnostic specific characters of the original plant are altered or destroyed, identification to species becomes difficult or impossible. Then gross morphological features of the source plant, i.e. growth habit, which are frequently critical for proper identification of the sample are, of course, not discernable. Finally, the structure of the wood offers numerous reliable characters to differentiate species, but wood is rarely if ever present in forensic material of *Cannabis.* (Anderson 1974).

Virtually no state or federal law takes into account that a mere botanical description or identification of *Cannabis sativa* (or any other species of *Cannabis*) carries with it the ability of the plant to produce hallucinogenic, euphoric or other effects in humans using it for such purposes. Consequently, a situation could conceivably come about in which a person may receive legal punishment for possessing material "identified" as *C. sativa,* when the substance is incapable of a drug abuse potential

because it contains none, or too little, of the chemical constituents to elicit the biological effect that the law was meant to control. The fact that strains of *C. sativa* have been found which are virtually devoid of Δ^8 and/or Δ^9-tetrahydrocannabinols, the active principles, is well documented in the scientific literature (Small 1979).

There is still disagreement concerning the botanical classification of *Cannabis*. It has been put into different families: in the Urticaceae (Nettle Family) in earlier periods; then into the Moraceae (Mulberry Family) during the last century and even today; finally, into a separate family—the Cannabaceae—together with *Humulus,* the hop plant, which assignment is now widely accepted. The major taxonomic problem, however, concerns the number of species in the genus—whether one or several. While botanists have generally tended to believe that *Cannabis* is monotypic, the polytypic concept is not new, going back to 1785. A number of Russian botanists have long held that *Cannabis* has at least three species. Schultes and co-workers (Schultes et al. 1974) have studied the problem in the literature, have examined hundreds of herbarium specimens, have studied plants from many parts of the world cultivated at the University of Mississippi and in the field in several localities, especially in Afghanistan. They are of the opinion that three species do exist: *C. sativa, C. indica* Lam. and *C. ruderalis* Jan. More recently, Anderson (Anderson 1974) studied the wood anatomy of *Cannabis.* Although few samples were examined, the magnitude of the differences was "impressive in a system as conservative as wood". His studies convinced him that he was dealing with two species: *C. sativa* and *C. indica.* Material of *C. ruderalis* was not then available. Emboden, who has also investigated *Cannabis* in the field and herbarium, has accepted the polytypic concept (Emboden 1974 and 1981).

Small has defended the monotypic concept, stating correctly: "It should be understood that the taxonomic debate concerning *Cannabis* represents the first rigorous examination of the implications of biological taxonomy for legislation." He then discussed for a forensic readership (Small 1976) the concepts involved in plant classification and nomenclature, the degree of subjectivity involved, ambiguities of biological names and the

extent and nature of taxonomic disagreements. His major point claims that the whole controversy is based on semantics, as indicated in the title: "The Forensic Taxonomic Dispute on *Cannabis:* Semantic Hokum". In a recent two-volume book, Small emphasizes again his belief that the biological question of whether the genus is monotypic or polytypic is merely one of semantics (Small 1979).

But, in a technical article in 1976, Small (Small 1976) meticulously summarizes his research in cytology and breeding behaviour, chemical variation, akene morphology and taxonomy, reaching the conclusion that *Cannabis* consists of one very variable species. This variation, he believes, is due primarily to human activity. He discerns two widespread classes: a northern group of "relatively limited intoxicant potential" and a more southern group of stronger intoxicant potential. These two groups are separated as distinct subspecies of *C. sativa.* Within each subspecies "two parallel phases"—the "weedy naturalized or indigenous" and the "cultivated or spontaneous"—are recognized as four named varieties.

Small has, in effect, accepted the proposition that the genus has several genetically stable entities, but he prefers to call them "subspecies" instead of "species" (Small 1979)—obviously representing a difference of weight in characters of classification (frequent in taxonomy) and approaching the category of "semantics", which he previously so strongly decried (Emboden 1981).

The whole legal problem could easily be solved if the law controlling "marihuana" were more logically worded to control "all species of *Cannabis*". Given the different viewpoints among botanists as to what constitutes a species, subspecies or variety, it may be long before agreement is reached in the taxonomic field, although almost all botanists who have recently considered the problem have concluded that the genus is indeed polytypic.

b. MONOTERPENOID CHROMENES OF CANNABIS. Since chemical studies on *Cannabis* have rarely, if ever, been published on the basis of vouchered specimens, these studies cannot be documented in a manner to permit unambiguous identification. We are obliged, therefore, to present a review of the chemical

constituents in this plant as if all specimens analyzed were referable *C. sativa,* realizing that this may or may not be the case. There is little dispute that the major active hallucinogen in *Cannabis* is Δ^9-tetrahydrocannabinol. To date, at least 50 cannabinoids, or rearranged cannabinoids, have been isolated from the genus. Most of these are trace constituents, and only a few are judged to be artefacts. The structures of the major cannabinoids are presented in Figures 2–11.

c. NON-CANNABINOID CONSTITUENTS OF CANNABIS. Although little is known of the contribution of non-cannabinoids to the biological activity of marihuana, the constituents recognized will be presented for the sake of completeness.

Flavonoids. Cosmosioside, orientin and vitexin (Paris and Paris 1973); and 2″-0-glucopyranosylorientin and 2″-0-glucopyranosylvitexin (Segelman et al. 1978).

Triterpenes. Epi-friedelanol, friedelanol and friedelin (Slatkin et al. 1971).

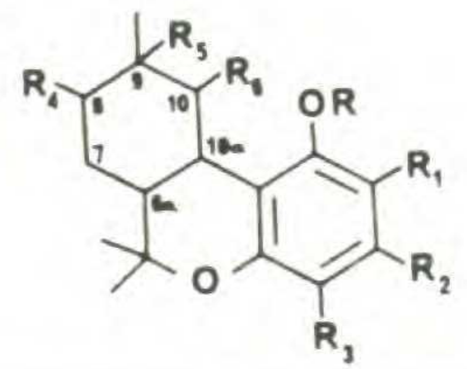
Sterols. Campesterol (Fenselau and Hermann 1982; Foote and Jones 1974; Slatkin et al. 1975a; and Turner and Mole 1973), β-sitosterol (Fenselau and Hermann 1972; Foote and Jones 1974; Itokawa et al. 1975; Slatkin et al. 1975a; Turner and Mole 1973); stigmasta-4,22-dien-3-one, stigmast-5-en-3-β-ol-7-one, stigmasta-5,22-dien-3-β-ol-7-one, campest-4-en-3-one and stigmast-4-en-3-one (Slatkin et al. 1975a); and ergosterol and 5 α-stigmasta-7,24(28)-dien-3β-ol (Novotny et al. 1976); 5α-stigmast-22-en-3-one, 5α-stigmasta-3-one, campesterol, and 5α-ergostan-3-one (Itokawa et al. 1975).

Essential Oil Analyses. Several monoterpenes, sesquiterpenes, phenylpropanoids and phenolic compounds (Bercht et al. 1971 and 1974; Hendriks et al. 1975; Hood et al 1973; Malingre et al. 1975; Stahl and Kunde 1973; Strömberg 1974).

Aliphatic Hydrocarbons. C_{22}-C_{31} *n*-alkanes (Adams and Jones 1973; Mobarak et al. 1974a, 1974b; and Rasmussen 1975); *iso*-alkanes C_{25}; C_{27} and C_{29} (Adams and Jones 1973) and *anteiso*-alkanes C_{26}, C_{28} and C_{30} (Adams and Jones 1973).

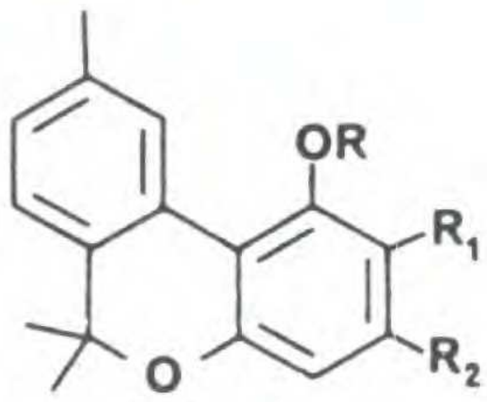
Fatty Acids. Several normal fatty acids have been reported (Itakawa et al. 1975; Romanenko 1974; Stepanova 1973).

Amino Acids, Proteins, Nucleosides. The following amino



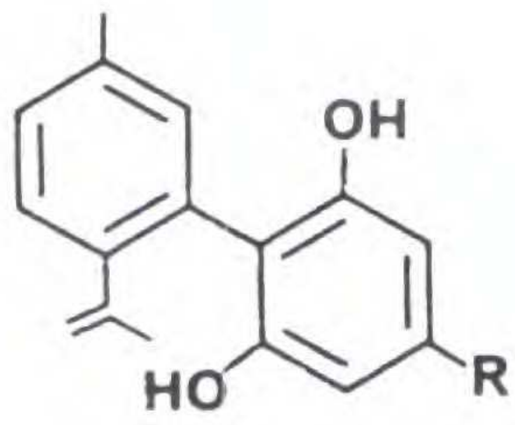
Cannabinoid	R	R_1	R_2	R_3	R_4	R_5	R_6	Other	References
(-)-trans-Δ^9-Tetrahyrocannabinol	H	H	C_5H_{11}	H	H	H	H	Δ^9	Gaoni and Mechoulam 1964a
$\Delta^{10(10a)}$-Tetrahydrocannabinol	H	H	C_5H_{11}	H	H	H	H	$\Delta^{10(10a)}$	Stromberg 1976
Δ^9-Tetrahydrocannabinolic Acid A	H	COOH	C_5H_{11}	H	H	H	H	Δ^9	Korte et al. 1965
Δ^9-Tetrahydrocannabinolic Acid B	H	H	C_5H_{11}	COOH	H	H	H	Δ^9	Mechoulam et al. 1969
Δ^9-Tetrahydrocannabinol Methyl Ether	CH_3	H	C_5H_{11}	H	H	H	H	Δ^9	Hanus 1974
3,4,-cin-Δ^9-Tetrahydrocannabinol	H	H	C_5H_{11}	H	H	H	H	Δ^9; 3,4-cis	Smith and Kempfert 1972
$\Delta^{10(10a)}$-Cannabitriol	H	H	C_5H_{11}	H	H	OH	OH	$\Delta^{10(10a)}$	Chan et al. 1976
(-)-trans-Δ^8-Tetrahydrocannabinol	H	H	C_5H_{11}	H	H	H	H	Δ^8	Gaoni and Mechoulam 1971
Δ^8-Tetrahydrocannabinolic Acid B	H	H	C_5H_{11}	COOH	H	H	H	Δ^8	Hanus 1974
Δ^8-Tetrahydrocannabitriol	H	H	C_5H_{11}	H	H	OH	OH	Δ^8	Stromberg 1976
(±)-$\Delta^{6a(10a)}$-Tetrahydrocannabinol	H	H	C_5H_{11}	H	H	H	H	$\Delta^{6a(10a)}$	Elsohly et al. 1978a
(±)-8,9-Dihydroxy-$\Delta^{6a(10a)}$-Tetrahydrocannabinol	H	H	C_5H_{11}	H	OH	OH	H	$\Delta^{6a(10a)}$	Elsohly et al. 1978a
(-)-10-Ethoxy-9-hydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol	H	H	C_5H_{11}	H	H	OH	O-Et	$\Delta^{6a(10a)}$	Elsohly et al. 1977
10-Oxo-$\Delta^{6a(10a)}$Tetrahydrocannabinol	H	H	C_5H_{11}	H	H	H	=O	$\Delta^{6a(10a)}$	Friedrich-Fiechtl and Spiteller 1975
Δ^9-Tetrahydrocannabivarol	H	H	C_3H_7	H	H	H	H	Δ^9	Merkus et al. 1971a
Δ^9-Tetrahydrocannabivarolic Acid	H	COOH	C_3H_7	H	H	H	H	Δ^9	Paris et al. 1973
Δ^9-Tetrahydrocannabiorcol	H	H	CH_3	H	H	H	H	Δ^9	Vree et al. 1971a

Figure 2. Cannabinoid Structures — THC Type



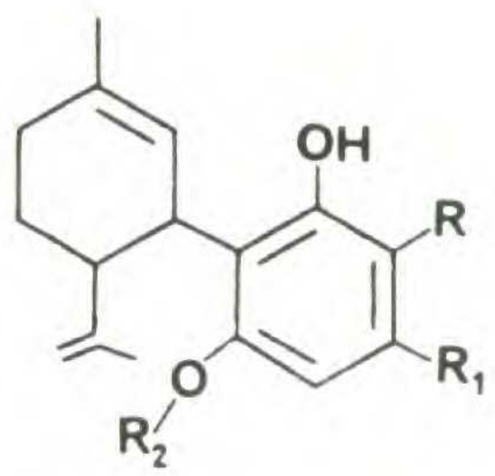
Cannabinoid	R	R_1	R_2	References
Cannabinol	H	H	C_5H_{11}	Adams et al. 1940
Cannabinolic Acid	H	COOH	C_5H_{11}	Mechoulam and Gaoni 1965
Cannabinol Methyl Ether	CH_3	H	C_5H_{11}	Bercht et al. 1973a
Cannabivarol	H	H	C_3H_7	Merkus 1971b Vree et al. 1971b
Cannabiorcol	H	H	CH_3	Vree et al. 1971a

Figure 3. Cannabinoid Structures — Cannabinol Type



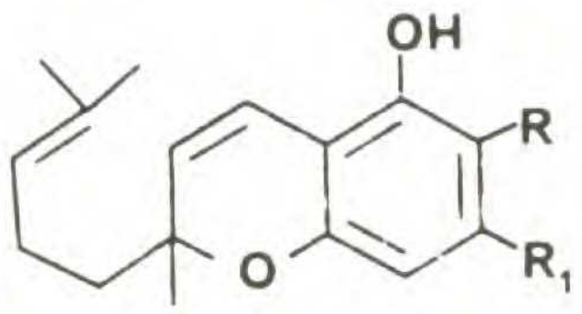
Cannabinoid	R	References
Cannabinodiol	C_5H_{11}	Van Ginneken et al. 1972; Lousberg et al. 1977
Cannabinodivarol	C_3H_7	Vree et al. 1972a

Figure 4. Cannabinoid Structures — Cannabinodiol Type



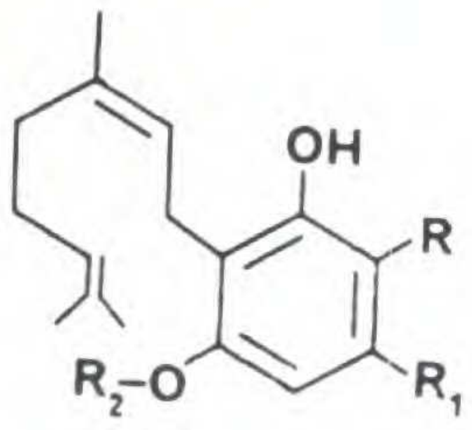
Cannabinoid	R	R_1	R_2	Reference
Cannabidiol	H	C_5H_{11}	H	Adams et al. 1940
Cannabidiolic Acid	COOH	C_5H_{11}	H	Krejci and Santavy 1975
Cannabidiol Monomethyl Ether	H	C_5H_{11}	CH_3	Shoyama et al. 1972a
Cannabidiolic Acid Monomethyl Ether	COOH	C_5H_{11}	CH_3	Shoyama et al. 1970
Cannabidivarol	H	C_3H_7	H	Vollner et al. 1969
Cannabidivarolic Acid	COOH	C_3H_7	H	Waller 1976
Cannabidiorcol	H	CH_3	H	Vree et al. 1971a

Figure 5. Cannabinoid Structures — Cannabidiol Type



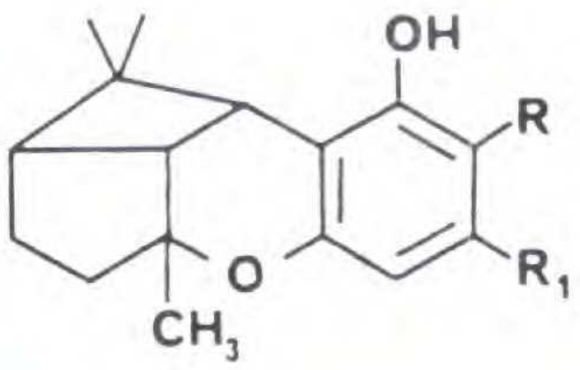
Cannabinoid	R	R_1	Reference
Cannabichromene	H	C_5H_{11}	Claussen et al. 1966b
Cannabichromenic Acid	COOH	C_5H_{11}	Shoyama et al. 1968
Cannabivarichromene	H	C_3H_7	de Zeeuw et al. 1973
Cannabichromevarol	OH	C_3H_7	Shoyama et al. 1975
Cannabichromevarolic Acid	COOH	C_3H_7	Shoyama et al. 1977

Figure 6. Cannabinoid Structures — Cannabichromene Type



Cannabinoid	R	R_1	R_2	References
Cannabigerol	H	C_5H_{11}	H	Gaoni and Mechoulam 1964b
Cannabigerolic Acid	COOH	C_5H_{11}	H	Mechoulam et al. 1969
Cannabigerol Monomethyl Ether	H	C_5H_{11}	CH_3	Yamuchi et al. 1968
Cannabigerolic Acid Monomethyl Ether	COOH	C_5H_{11}	CH_3	Shoyama et al. 1970
Cannabigerovarol	H	C_3H_7	H	Shoyama et al. 1975
Cannabigerovarol Monomethyl Ether	H	C_3H_7	CH_3	Bercht et al. 1973a
Cannabigerovarolic Acid	COOH	C_3H_7	H	Shoyama et al. 1977

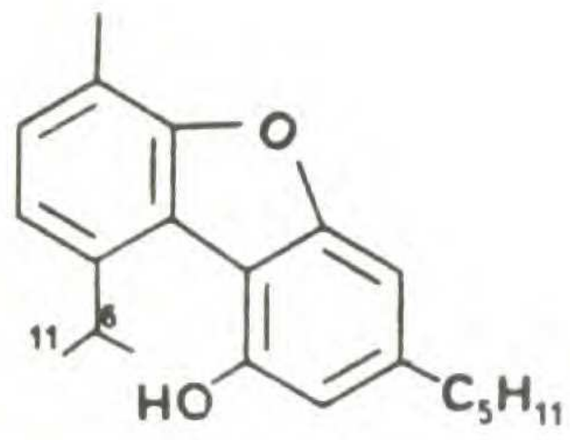
Figure 7. Cannabinoid Structures — Cannabigerol Type



Cannabinoid	R	R_1	References
*Cannabicylol (Cannabipinol)	H	C_5H_{11}	Claussen et al. 1967
*Cannabicyclolic Acid	COOH	C_5H_{11}	Shoyama et al. 1972b
Cannabivaricyclol	H	C_3H_7	Vree et al. 1972a, 1927b

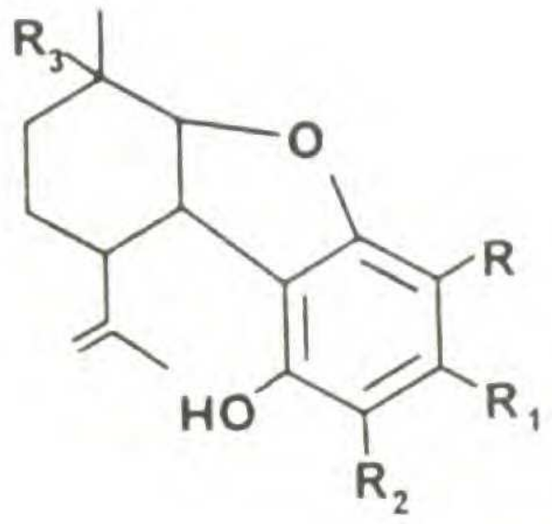
*Probably artifacts

Figure 8. Cannabinoid Structures — Cannabicyclol Type



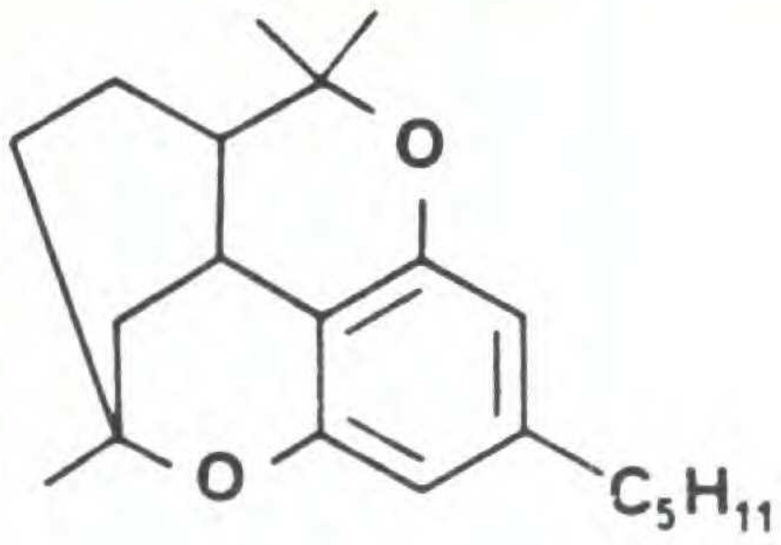
Cannabinoid		Reference
Cannabifuran		Friedrich-Fiechtl and Spiteller 1975
Dehydrocannabifuran	$\Delta^{6(11)}$	Friedrich-Fiechtl and Spiteller 1975

Figure 9. Cannabinoid Structures — Cannabifuran Type

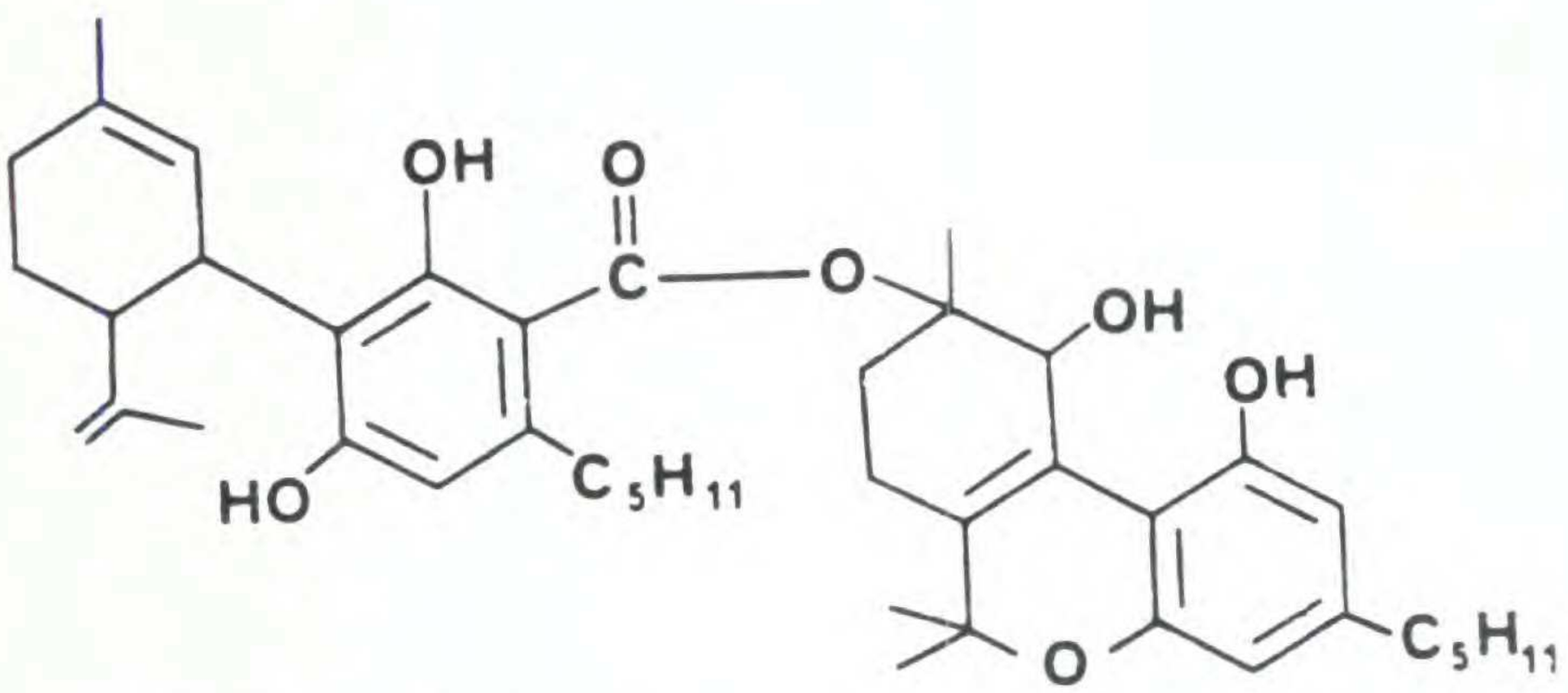


Cannabinoid	R	R_1	R_2	R_3	Reference
Cannabielsoic Acid A	H	C_5H_{11}	COOH	OH	Shani and Mechoulam 1974
Cannabielsoic Acid B	COOH	C_5H_{11}	H	OH	Shani and Mechoulam 1974
Cannabielsoin	H	C_5H_{11}	OH	OH	Bercht et al. 1973a
C_3-Cannabielsoin	H	C_3H_7	OH	OH	Grote and Spiteller 1978a
C_3-Cannabielsoic Acid B	COOH	C_3H_7	H	OH	Grote and Spiteller 1978a

Figure 10. Cannabinoid Structures — Cannabielsoin Type



Cannabicitran (Bercht et al. 1974)



Cannabidiolic Acid Tetrahydrocannabitriol Ester (von Spulak et al. 1968)

Figure 11. Cannabinoid Stuctures — Miscellaneous Types

acids have been identified in *Cannabis:* alanine, aspartic acid, glutamic acid, glycine, serine, arginine, isoleucine, phenylalanine, proline and tyrosine (Paris et al. 1975); cystine, methionine and tryptophan (Wallace et al. 1973); and histidine, leucine, lysine, threonine and valine (Obata et al. 1960). The amino acid sequence of hemp cytochrome-C has been reported as Lys-Thy-Lys-Cys-Ala-Glu-Cys-His-Thr-Val-Gly-Arg-Gly-His (Wallace et al. 1973).

The fruits of *Cannabis* are reported to contain edestin (St. Angelo et al. 1969; Stockwell et al. 1964); zeatin and zeatin nucleoside (Rybicka and Engelbrecht 1974); edestinase (St. Angelo et al. 1969) and glucosidase (emulsin) (Leoncini 1931). *Cannabis* leaves have yielded a water-soluble glycoprotein (Hillestad and Wold 1977; Hillestad et al. 1977a), and the dormant

cotyledons of *Cannabis* contain adenosine-5-phosphatase (Bargoni and Luzzati 1956).

Cyclitols and Sugars. Arabinitol, bornesitol, erythritol, fructose, glucose, glycerol, D-manno-heptulose, altro-heptulose, (+)-inositol, myo-inositol, D-glycero-D-manno-cotulose, ribitol, sucrose and xylitol (Haustveit and Wold 1973); quebrachitol (Adams et al. 1940; Haustveit and Wold 1973; and Krishnamurty and Kaushal 1976); galactosamine (the first record in higher plants) (Wold and Hillestad 1976) and vomifoliol and dihydrovomifoliol (Bercht et al 1976a); and glucose, fructose, galactose, myo-inositol, galactitol and mannitol (Krishnamurty and Kaushal 1976).

Phenolics. *p*-Coumaric, *p*-hydroxybenzoic and vanillic acids (Paris and Paris 1973); and *p*-vinylphenol (probably an artefact) (Burstein et al., 1976).

Alkaloids and Related Substances. Cannabamines A, B, C and D (structures undetermined) (Klein et al. 1971; Caolo et al. 1979a and 1979b) have reported on the isolation of afileramine, an alkaloid from *Zanthoxylum punctatum* Vahl bearing a direct structural relationship to the cannabinols. A second cannabinol-like alkaloid was isolated by these workers from the same plant, which presented an identical mass spectrometric fragmentation as cannabamine B, and a structure was postulated; cannabisativine (Lotter et al. 1975; Slatkin et al. 1975b, Turner et al. 1976), anhydrocannabisativine (Elsohly et al. 1978b); hexadecanamide (Smith and Kempfert 1977); piperidine (Obata et al. 1960; Salemink et al. 1966 and Bercht and Salemink 1969); hordenine (El-Feraly and Turner 1975; and Elsohly and Turner 1976 and 1977); ammonia, methylamine, ethylamine, *n*-propylamine, *n*-butylamine, *iso*-butylamine, *sec*-butylamine, dimethylamine, diethylamine and pyrrolidine (Lousberg and Salemink 1973), with the following being tentatively identified: *iso*-amylamine, β-phenylethylamine, *n*-pentylamine, cadaverine, ethnolamine (or histamine) and benzylamine (or tyramine) (Lousberg and Salemink 1973); choline (El-Feraly and Turner 1975; Mole and Turner 1973, 1974; Salemink et al. 1966; and Turner and Mole 1973); neurine (El-Feraly and Turner 1975; Mole and Turner 1973, 1974; Shoyama et al. 1968; and Turner and Mole 1973);

trigonelline (Mole and Turner 1974; Salemink et al. 1966; Schulze and Frankfurt 1894); N-(*p*-hydroxy-*β*-phenethyl)-*p*-hydroxy-*trans*-cinnamide (Slatkin et al. 1971); and L-(+)-isoleucine betaine (Lousberg and Salemink 1973).

Spiro-compounds. Recently, several spiro-compounds have been isolated from *Cannabis sativa* of various geographical origins, such as cannabispirone (El-Feraly et al. 1977; Bercht et al. 1976b); dehydrocannabispiran (cannabispirenone) (Bercht et al. 1976b); cannabispiranol (*β*-cannabispiranol) (Boeren et al. 1977; Crombie et al. 1978); cannabispiradienone (Crombie et al. 1979) and acetyl cannabispiranol (Shoyama and Nishioka 1978).

Dihydrostilbenes. A group of substituted dihydrostilbenes of biogenetic interest has been isolated from *Cannabis sativa,* including cannabiprene, 3,3′-dihydroxy-4,5′-dimethoxybibenzyl and 3,4′-dihydroxy-5-methoxybibenzyl (Crombie and Crombie 1978) and 3′,4′-dihydroxy-5,5′-dimethoxy-3-(3-methylbut-2-enyl)-bibenzyl (Kettenes-van den Bosch et al. 1978).

Phenanthrenes. A single example of a phenanthrene derivative has been isolated from *Cannabis sativa,* which has been named cannabidihydrophenanthrene (Crombie et al. 1979).

Coumarones. Two coumarone derivatives, cannabicoumarononе and cannabicoumarononic acid (Grote and Spiteller 1978b) have recently been isolated from *Cannabis sativa.*

Current information suggests that *Cannabis* exists as three main phenotypes (Fetterman et al. 1971). Type I contains usually 0.3% of Δ^9-THC, and these plants most frequently originate from countries south of latitude 30° N. Type I contains also low amounts of cannabidiol (0.5%). Type II *Cannabis* likewise usually has a high Δ^9-THC content (0.3%), but more than 0.5% cannabidiol. Type III *Cannabis* in general has 0.3% Δ^9-THC and 0.5% cannabidiol. Both types II and III appear to originate in countries north of latitude 30° N. To date, no one has correlated cannabinoid content with definite taxonomic concepts.

d. PHARMACOLOGY OF CANNABIS. The public uproar surrounding *Cannabis* and its constituents represents a classic example of legal hindrance to drug development. Societal, political factors and irresponsible publicity have compounded the problem.

Research into potential new medical uses of cannabinoids has probably been reduced as a result of the hindrances imposed by legal restraints on the study of *Cannabis*. Yet this research is promising. For example, Δ^9-THC has been reported to be very effective in reducing many of the side effects attendent upon the administration of potent antitumour chemotherapy in humans (Davies et al. 1974; Sallan et al. 1975). Likewise, the beneficial effect of *Cannabis* smoking in the treatment of glaucoma is difficult to dismiss (Hepler and Frank 1971; Hepler et al. 1972; Shapiro 1974). The analgesic (Buxbaum 1972; Bicher and Mechoulam 1968; Cortex Jr. et al. 1966; Kaymakcalan et al. 1974; Kosersky et al 1973; Parker and Dubas 1972), antiinflammatory (Kosersky et al. 1973; Sofia et al. 1974), anticonvulsant effects (Carlini et al. 1973; Cely et al. 1974; Chesher and Jackson 1974; Conscroe and Man 1973; Conscroe et al. 1973; Corcoran et al. 1973; Karler 1973; Karler et al. 1973, 1974; Man and Conscroe 1973; McCaughran et al. 1974; Mincs et al. 1973; Sofia et al. 1971; Tannhauser and Izquierdo 1974; Turkanis et al. 1974; Wada et al. 1973), and antitumour activity (Bhargava 1978; Braude and Szara 1976a, 1976b; Carchman et al. 1976; Desoize and Nahas 1976; Harris et al. 1974, 1976) of certain of the cannabinoids in laboratory animals might justify clinical trial in man. It has been suggested that *Cannabis* might be useful as an agent in rehabilitating alcoholics (Scher 1971) and in the treatment of asthma (Arey 1973) as well as for other conditions (Beaconsfield et al. 1975). In addition, recently reported effects of certain of the cannabinoids in the inhibition of naloxone-induced withdrawal in morphine-dependent animals may offer promise in the treatment of narcotic addiction (Bhargava 1976a and b).

Pharmaceutical firms and other entities are actively engaged in synthesizing analogs of the cannabinoids, (Pars et al. 1976; Razdan and Dalzell 1976; Razdan et al. 1976a, 1976b; Winn et al. 1976; Kurth et al., 1976), instead of further exploring uses of the natural parent compounds. Patent difficulties and stability problems of the natural derivatives as well as legal and political implications have no doubt played an important role in this decision.

Mechoulam and co-workers (1976) have summarized the current status of our knowledge of structure-activity relationships in the cannabinoid area. With regard to psychotomimetic activity, the structural requirements may be summarized as follows:

1. A benzopyran (or xanthene) type of structure with a hydroxyl group at the 1 aromatic position and an alkyl group on the 3 aromatic position seem to be required. Opening of the pyran ring leads to complete loss of activity.

2. The aromatic hydroxyl group has to be free or esterified. Blocking of the hydroxyl group as an ether inactivates the molecule.

3. When alkyl groups are substituted on the phenolic ring at C-3, activity is retained. Substitution at C-5 eliminates activity. Electronegative groups such as carboxyl, carbomethoxyl and acetyl at either C-3 or C-5 eliminate activity.

4. A certain length of the aromatic side chain at C-3 is a requirement for activity. Branching of the side chain may lead to substantial increase in potency. A 1,2-dimethylheptyl or a 1,1-dimethylheptyl side chain seems to be best.

5. Not all of the theoretically possible THC's are active. Thus, Δ^8 and Δ^9-THC are active in the 3R,4R series only; Δ^7-THC and Δ^{11}-THC are inactive; Δ^{10a}-THC is active; Δ^9-3,4-*cis*-THC is inactive.

6. The terpenoid and pyran rings may be considerably modified. These modifications do not seem to follow a regular pattern, and even tentative rules cannot yet be put forward.

e. NEW POTENTIAL HAZARD OF MARIHUANA USE. Recent attempts to increase the "potency" of marihuana by spraying whole growing plants with liquid fertilizer have been reported. It has been pointed out that this practice could be dangerous on the theoretical grounds that such treatment might cause the formation of carcinogenic N-nitrosamines (Farnsworth and Cordell 1976). Fertilizers containing nitrate can potentially initiate N-nitroso derivitization of secondary amines known to be present in marihuana, with the reaction being accelerated by the presence of any compounds with *o*-hydroxy phenolic (catechol) groups. It has recently been shown that marihuana does contain

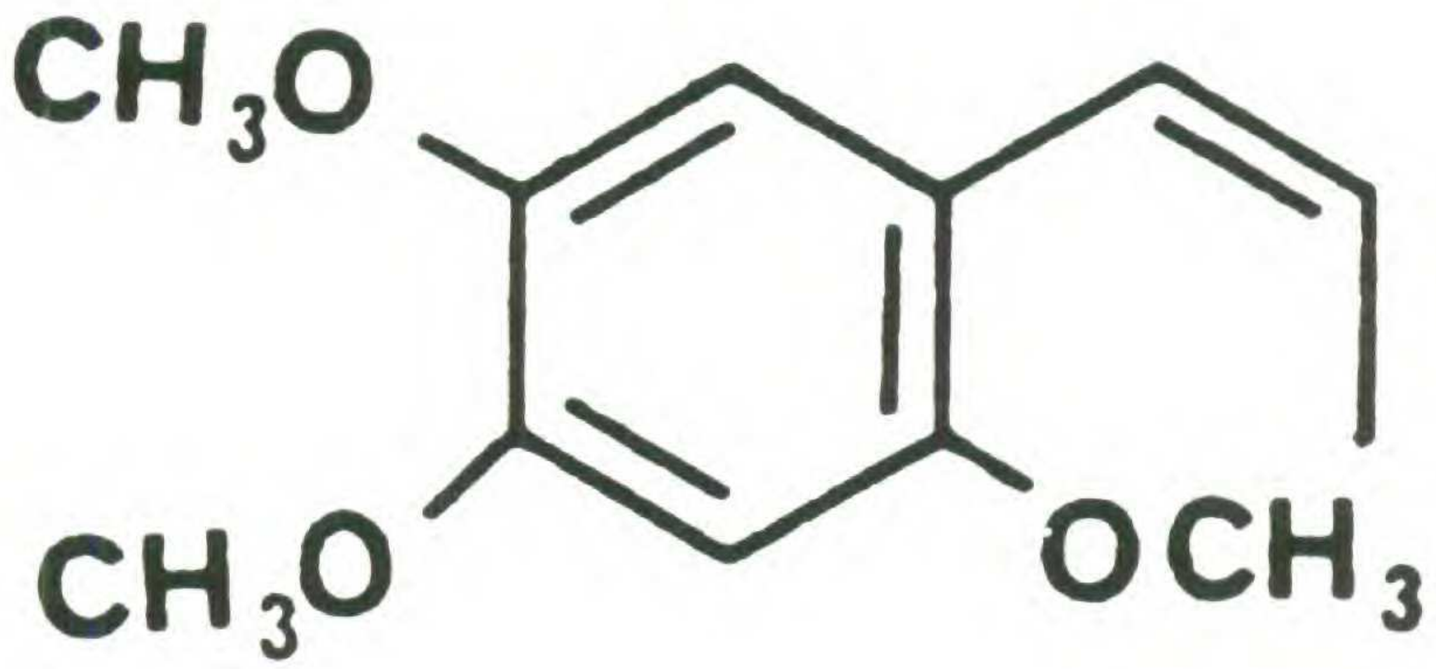
at least one flavonoid with the *o*-hydroxy phenolic moiety. Thus, on theoretical grounds, one would predict the formation of carcinogenic N-nitroso compounds in marihuana treated with nitrate-containing liquid fertilizers. The implications of this possibility are obvious.

2. Phenylpropenes

Araceae

Acorus L.

There is some evidence that Indians of northern Canada chew the root of *Acorus Calamus* L.—*flag root, rat root, sweet calomel*—for its medicinal and stimulant properties. In excessive doses, this root is known to induce strong visual hallucinations (Hoffer and Osmund 1967). The hallucinogenic principles are reported possibly to be α-asarone (I) and β-asarone (II) (Schultes 1970c). There are two species of *Acorus* occurring in the north temperate zone and in the warmer parts of both hemispheres.



I

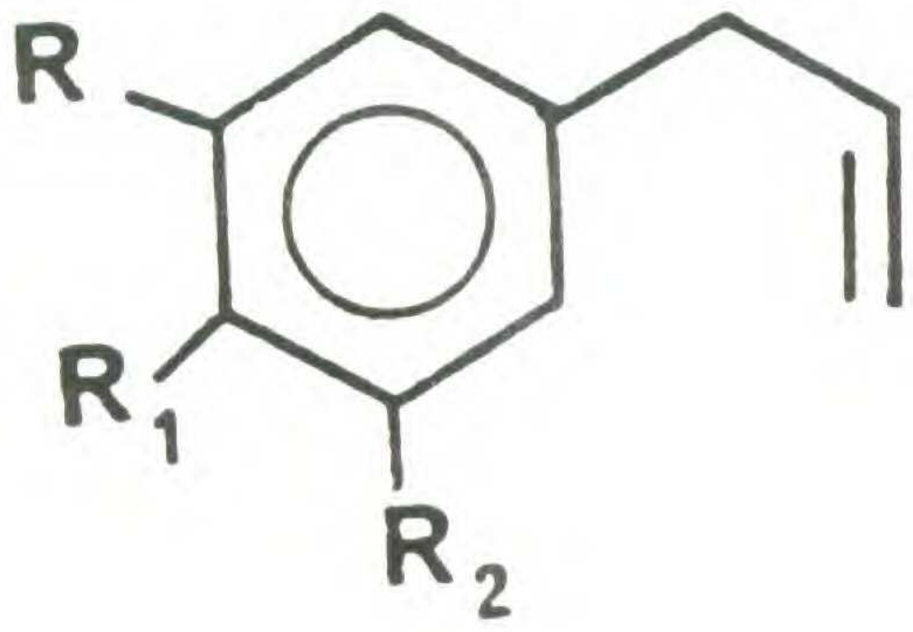
II (Geometric isomer of I)

Myristicaceae

Myristica Gronov.

The tree that yields the spices nutmeg and mace—*Myristica fragrans* Hout.—is thought to have been employed aboriginally as a narcotic in southeastern Asia, where it is native. It is sometimes used as an hallucinogen in sophisticated circles in Europe and North America and has occasionally become a problem in prisons in the United States (Panayotopoulos and Chisholm 1970; Weil 1965, 1966, 1967; Weiss 1960; Williams and West 1968). The toxicity of nutmeg, when either accidentally or knowingly ingested, is well documented (Green Jr. 1959; Painter et al. 1971; Payne 1963).

Although the toxicology of nutmeg has not yet been fully explained, the psychoactive principles are associated probably with the essential oil present in the seed and aril. The composition of the essential oil is highly variable, both qualitatively and quantitatively, but it does contain fatty acids, terpenes and aromatic compounds, especially arylbenzenoid derivatives. The major constituents of the essential oil appear to be elemicin (III), myristicin (IV) and safrole (V). Undoubtedly, all three of these compounds contribute to the psychotomimetic effect of nutmeg. All of these compounds can be visualized as precursors of amphetamines and might exert a sympathomimetic effect following biotransformation. When nutmeg essential oil was injected into mice, a strong psychotomimetic effect was observed, which was greater than that produced by myristicin alone (Kalbhen 1971).



	R	R_1	R_2
III	OCH_3	OCH_3	OCH_3
IV	$-O-CH_2-O-$		OCH_3
V	$-O-CH_2-O-$		H

Preliminary evaluation of elemicin (Schlemmer et al. 1973) has shown that it produces the same behavioural effect in mice as do many of the known hallucinogens, when evaluated by the Corne and Pickering model (Corne and Pickering 1967). This observation suggests that elemicin, in addition to myristicin (Shulgin et al. 1967; Truitt et al. 1961), contributes to the psychotomimetic effect of nutmeg.

It should be emphasized that safrole is a known weak carcinogen (Farnsworth et al. 1976) and that prolonged use of nutmeg or other materials containing safrole could have serious implications.

For hallucinating purposes, ground nutmeg is taken orally in large doses, usually several teaspoonsful. The effects vary appreciably but are often characterized by distortion of perception of time and space, dizziness, tachycardia, dry mouth, headache and occasionally visual hallucinations (Forrest and Heacock 1972; Kalbhen 1971; Weil 1965, 1966, 1967).

Myristicin has been identified as a component of cigarette smoke (Schmeltz et al. 1966).

Myristica is a genus of some 120 species of the Old World tropics. The only commercially important species is *M. fragrans,* native of the Moluccas and source of two products: nutmeg from its seeds, and mace from the aril surrounding the seed.

NITROGENOUS PRINCIPLES

1. β-CARBOLINES

Malpighiaceae

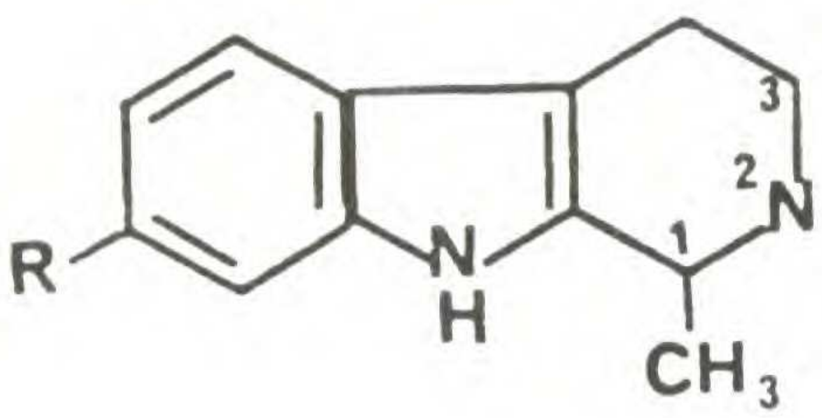
Banisteriopsis C.B. Rob. & Small

In wet tropical forest areas of northern South America, the aborigines use as hallucinogens several species of *Banisteriopsis* containing harmala alkaloids: *B. Caapi* (Spr. ex Griseb.) Mort., *B. inebrians* Mort. An intoxicating drink is prepared from the bark of the stems in the Amazon of Brazil, Bolivia, Colombia, Ecuador and Peru, the Orinoco of Venezuela and the Pacific coast of Colombia. It is variously known as *ayahuasca, caapi, yajé, natema, pindé*, or *dapa.* Usually, only one species enters the preparation, but frequently admixtures of other plants are employed (Friedberg 1965; Rivier and Lindgren 1972; and Schultes 1957, 1961b).

A genus of some 100 species of tropical America, *Banisteriopsis* is taxonomically still rather poorly understood. The classification of *B. Caapi* and *B. inebrians* is particularly confused, primarily because of the sparcity of fertile material for study of these infrequently flowering jungle lianas, even though the earliest botanical attention to this drug plant dates from 1852, when it was first encountered in northwestern Brazil by the explorer Spruce (Schultes 1957, 1966b, 1979a,b).

The chemistry of these hallucinogenic species of *Banisteriopsis* has been more critically investigated than the taxonomy, yet the failure of chemists to insist upon botanically determined and vouchered material for analyses has created chaos. Earlier workers, isolated alkaloidal constituents which they named telepathine, yageine and banisterine from plants referable probably to *B. Caapi.* All of these alkaloids were eventually identified as harmine (VI). More recent examination of botanically authenticated material of this species has established the presence

in the bark—and sometimes in the leaves—of harmine as well as occasional lesser amounts of harmaline (VII) and (±)-tetrahydroharmine (VIII) (Chen and Chen 1939; Deulofeu 1967). Investigations of *B. inebrians* in more recent years have yielded harmine from the stems as well as minute amounts of what appears to be harmaline (O'Connell and Lynn 1953). An interesting chemical study of stems of the type collection of *B. Caapi* has indicated, in spite of the passage of some 115 years, the presence of harmine in concentrations matching that of freshly collected material (Schultes et al. 1969). Several new harman-type bases have been reported in *B. Caapi* by Japanese workers, including acetyl norharmine, ketotetrahydronorharmine, harmic amide, harmalinic acid, harmic acid methyl ester and harmine-N-oxide (Hashimoto and Kawanishi 1975, 1976).



	R	Other
VI	OCH_3	Δ^1, Δ^3
VII	OCH_3	Δ^1
VIII	OCH_3	-N-H
IX	H	Δ^1, Δ^3

While *Banisteriopsis Caapi* is normally employed as a drink, recent indirect evidence from the northwest Amazon indicates that it may also be used as a snuff. Harmala alkaloids have been reported from snuff powders prepared from a vine said to be the source of an intoxicating drink, but voucher botanical specimens are lacking (Holmstedt and Lindgren 1967).

Harmine has been isolated from *Cabi paraensis* Ducke of the eastern Amazon. *Cabi* is a genus closely allied to *Banisteriopsis*.

While the plant is valued in folk medicine, it is apparently not employed as an hallucinogen (Schultes 1970c).

Banisteriopsis argentea (Spreng. ex. A. Juss.) Mort., an Indian species, has been shown to contain tetrahydroharman, 5-methoxytetrahydroharman, harmine and harmaline, and a novel related β-carboline, leptaflorine (Ghosal et al. 1971), but this species does not appear to have been used as an hallucinogen.

Solanaceae

Nicotiana L.

It is well established that *tobacco* (*Nicotiana* spp.) has been used for hallucinatory purposes for centuries. Substantive evidence for the effect is lacking, however: the normal *Nicotiana* alkaloids, i.e. nicotine, etc., hardly offer an explanation. Recently, Janiger and Dobkin de Rios (1976) have raised the question as to whether or not the substantial quantities of two well known hallucinogens, i.e. harman (IX) and norharman (10–20 mcg. per cigarette), are absorbed into the blood stream during the smoking process. They also raise the question as to whether the tobacco products used by aborigines, who have been primary users of tobacco products for hallucinogenic purposes, would produce harman and norharman, since their tobacco products would probably have been cured in a different manner than tobacco currently used in western society. These two bases are pyrosynthesized and do not exist as such in normal tobacco. Certainly this challenge should encourage analysis of the blood of tobacco users in an effort to support or deny such an hypothesis (Janiger and Dobkin de Rios 1976).

Zygophyllaceae

Peganum L.

The *Syrian rue* or *Peganum Harmala* L. is an herb found in dry localities from the Mediterranean area east to India, Mongolia and Manchuria. It is a member of a genus of six species distributed in dry areas of Asia Minor and Asia and in southwestern United States and Mexico. Although this and other species of *Peganum* have long been esteemed in folk medicine, its purposeful employment as an hallucinogen is open

to question, vague reports notwithstanding, even though it does have psychotomimetic principles (Porter 1962). It has recently been suggested that the famous soma of ancient India might have been *P. Harmala* (Flattery 1978). The pharmacology of harmine (Beer 1939) and related bases has been reviewed (Naranjo 1967).

The seeds of *Peganum Harmala* contain harmine, harmaline, harmalol, harmol, harman, peganine, isopeganine, dipegine, vasicinone and deoxyvasicinone, bases of a typical β-carboline structure of wide botanical and geographical distribution, having been isolated from at least 27 plant families of both the New and the Old World (Kurbanov and Zharekeev 1974; Mirzakhmedov et al. 1975; Zharekeev et al. 1974).

2. ERGOLINES

Convolvulaceae

Ipomoea L. and *Turbina* Raf.

The early Spanish chroniclers of Mexico reported that the Indians employed in their religious and magic rites an hallucinogenic seed called *ololiuqui* by the Aztecs. It was also used medicinally and was said to have analgesic properties when applied as a poultice.

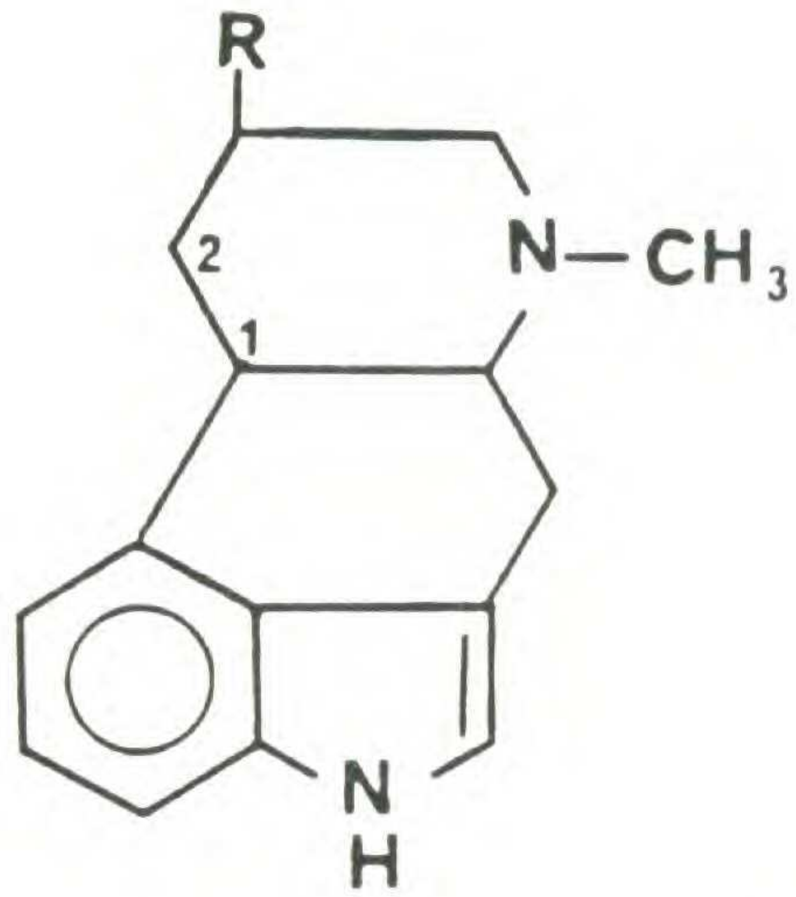
Known as *coatl-xoxouhqui* ("snake plant"), the plant was adequately illustrated as a morning glory. Although several Mexican botanists accepted this identification during the last century, not until 40 years ago was a voucher specimen of a convolvulaceous plant, the seeds of which were employed as a divinatory hallucinogen, collected amongst the Mazatecs of Oaxaca and determined as *Turbina corymbosa* (L.) Raf. (formerly known as *Rivea corymbosa* (L.) Hall. f.). Later, field work uncovered similar uses of another morning glory, *Ipomoea violacea* L., amongst the Zapotecs, also of Oaxaca where it is called *badoh negro;* this species represents possibly the narcotic *tlitliltzin* of the ancient Aztecs (MacDougall 1960a; Schultes and Hofmann 1973, 1980).

In the interval, *ololiuqui* had been identified as a species of *Datura,* an identification that gained wide acceptance (Safford 1916b). The reasoning on which this theory was based held that

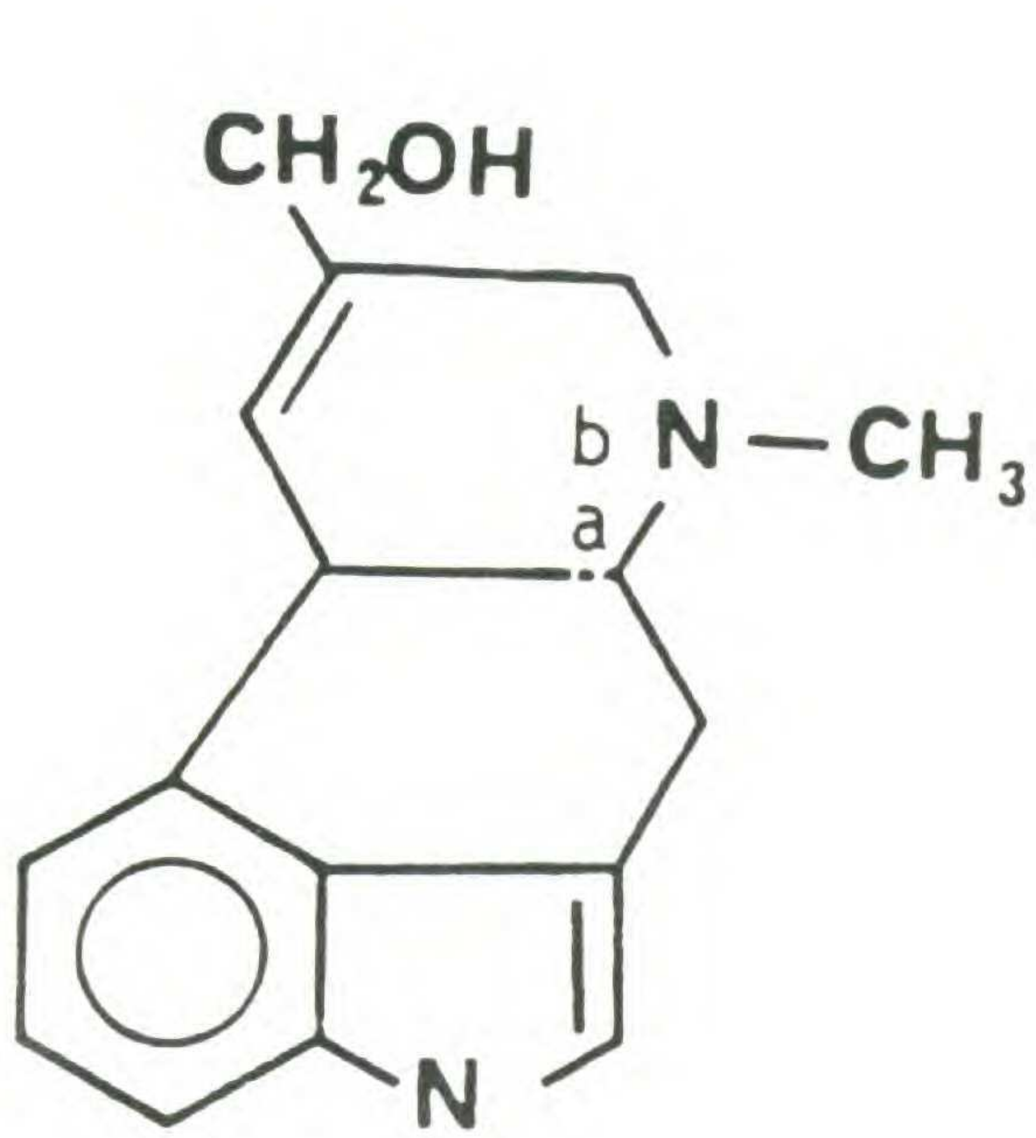
in four centuries no narcotic use had been observed for a morning glory; that the convolvulaceous flowers resembled those of *Datura* and might have led to confusion; and that descriptions of ololiuqui-intoxication coincided closely with that induced by *Datura; Datura* had been and still is employed as a divinatory narcotic in Mexico; and, most significantly, no psychoactive principle was known from the Convolvulaceae.

Experimental psychiatry indicated that *Turbina* was definitely hallucinogenic (Osmond 1955), supporting ethnobotanical field work (Schultes 1970c). Yet chemists were unable to isolate any inebriating constituents until 1960, when ergot alkaloids related to the synthetic hallucinogenic compound LSD were found in the seeds of both *T. corymbosa* and *Ipomoea violacea.*

The main psychotomimetic constituent of the seeds of both species are ergine (*d*-lysergic acid diethylamide) (X) and isoergine (*d*-isolysergic acid diethylamide) (XI) which occur together with minor alkaloids: chanoclavine, (XII), elymoclavine, (XIII), and lysergol (XIV). Ergometrine appears to be present in seeds of *Ipomoea violacea* but absent in *Turbina corymbosa.* The total alkaloid content of *T. corymbosa* seed is 0.012%; of *I. violacea,* 0.06%—and, indeed, Indians use smaller quantities of the latter than of the former (Hofmann 1961, 1963).



	R	Other
X	-CO-NH_2	Δ^1
XI	..CO-NH_2	Δ^1
XIV	-CH_2OH	Δ^2



XII	Seco a,b
XIII	

a. *The Discovery of Ergot Alkaloids.*—Constituents of *ergot, Claviceps purpurea* (Fr.) Tul., a relatively primitive ascomycete, in one of the phylogenetically most advanced angiosperm families was unexpected and is of great chemotaxonomic interest. Suspicion that fungal spores might have contaminated the convolvulaceous seeds was experimentally ruled out (Taber and Heacock 1962), and the discovery of the same alkaloids in fresh leaves, stalks, and root of *Ipomoea violacea* and, to a minor extent, in leaves of *Turbina corymbosa* indicated that these constituents are produced by the tissue of the morning glories themselves, not by infecting fungi (Shinners 1965).

Studies have shown the presence of these ergot alkaloids in a number of horticultural "varieties" of *Ipomoea violacea* and other species of *Ipomoea,* as well as in the related genera *Argyreia* and *Stictocardia* (Chao and Der Marderosian 1973; Der Marderosian and Youngken Jr. 1966; Hylin and Watson 1965; Taber et al. 1963).

There are folklore references to psychotomimetic uses of *Ipomoea carnea* Jacq. in Ecuador, where its common names, *borrachera* and *matacabra,* refer to its inebriating or toxic effects. Ergot alkaloids have been isolated from this species (Lascano et al. 1967; Naranjo, 1969; Naranjo et al. 1964).

The nomenclature and taxonomy of the Convolvulaceae are in a state of extreme confusion, especially as to delimitation of genera (Der Marderosian 1965; Schultes 1970c, 1980; Shinners 1965). *Turbina corymbosa* occurs in the southernmost United States, Mexico and Central America, some of the Caribbean islands and the northern coast of South America. It has at least nine synonyms, of which *Ipomoea sidaefolia* (HBK.) Choisy and *Rivea corymbosa* are the most frequently employed. *Ipomoea,* comprising upwards of 500 species in the warm temperate and tropical parts of the hemisphere, is a genus of climbing herbs or shrubs, rarely semi-aquatic. *Ipomoea violacea,* often referred to by its synonyms *I. rubrocaerulea* Hook. and *I. tricolor* Cav., is represented in horticulture by a number of "varieties", such as Heavenly Blue, Pearly Gates, Flying Saucers, Wedding Bells, Summer Skies, and Blue Stars — all of which contain the hallucinogenic ergot alkaloids (Der Marderosian 1967b).

The hallucinogenic effects of the ergot alkaloids have been known for centuries in Europe. *Claviceps purpurea,* parasitic on rye and other grasses, has long been used medicinally by midwives in cases of difficult childbirth, since ergot acts to induce contractions of involuntary muscle and, as a strong vasoconstrictor, to help reduce postpartem hemorrhage. During the Middle Ages, in rye-consuming areas of Europe, periodic poisoning of whole villages with ergotism occurred. Those who ate rye bread contaminated with ergot frequently suffered gangrene and loss of limbs, hallucinations, permanent insanity, and death. The cause of these epidemics was discovered only during the 17th Century (Schultes and Hofmann 1980).

While ergot has probably never been purposefully used as an hallucinogen in Europe, an interesting hypothesis has been offered that a species of ergot, *Claviceps paspali* (Schw.) Stevens & Hall, may have played a role in the Mysteries of Eleusis in ancient Greece, secret rituals which have long puzzled classical scholars (Wasson, Hofmann and Ruck 1978).

3. IBOGA INDOLES

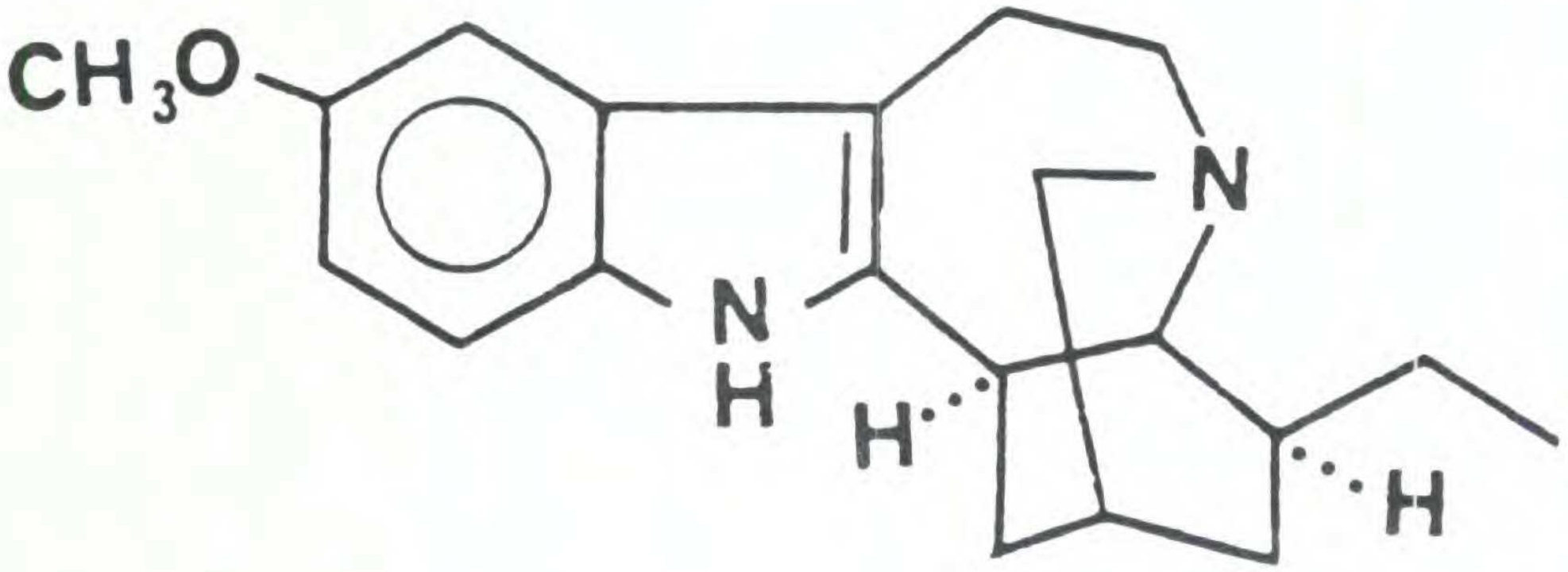
Apocynaceae

Tabernanthe Baill.

Probably the only member of this alkaloid-rich family known definitely to be utilized as an hallucinogen is *iboga,* the yellowish root of *Tabernanthe Iboga* Baill. This narcotic is of great social importance, especially in Gabon and nearby portions of the Congo in Africa. The religious use of iboga, early reported by French and Belgian explorers in the middle of the last century, appears to be spreading. In Gabon, it is employed in initiation rites of secret societies, the most famous of which is the Bwiti Cult. Sorcerers take the drug before communicating with the spirit world or seeking advice from ancestors (Fernandez 1972; Pope 1969).

Twelve closely related indole alkaloids have been reported from iboga; they comprise up to 6% of the dried roots. Ibogaine (XV), apparently the principal psychoactive alkaloid, acts as a cholinesterase inhibitor, a strong central stimulant and as an hallucinogen (Dybowski and Landrin 1901; Haller and Heckel

1901; Hoffer and Osmund 1967; Pope 1969; Schneider and Sigg 1957).



XV

Tabernanthe is a genus of about seven species native to tropical Africa.

Sometimes other plants — occasionally as many as 10—are taken with *iboga,* but few have been botanically identified or chemically investigated. One of the most interesting, the euphorbiaceous *Alchornea floribunda* Muell.-Arg., is employed in the same way as iboga in another secret society in Gabon, but it may not be hallucinogenic. Its active principle has been thought to be the indole yohimbine (Fernandez 1972; Schultes 1970c), an unusual taxonomic occurrence for this base; recently, alchorneine, isoalchorneine and alchorneinone have been reported from this species (Khuong-Huu, Le Forestier and Goutarel 1972)

4. ISOXAZOLES

Agaricaceae

Amanita L.

Amanita muscaria (L. ex Fr.) Pers. ex W.J. Hook.—the *fly agaric,* a mushroom of the north-temperate zone of Eurasia and

North America—may represent one of the oldest of the hallucinogens used by man, and only very recently has a clarification of the chemistry of its active principles begun to take shape (Eugster 1967; Heim 1963b).

The Aryan invaders of India 3500 years ago worshipped a plant, the god-narcotic *soma,* centre of an elaborate cult in which the inebriating juice was ceremonially drunk (Wasson 1968). More than 1000 hymns to *soma* have survived in the Rig Veda, describing the plant and its significance in detail. The use of soma died out 2000 years ago. Botanists have proposed more than 100 species in attempts to identify soma, but none have been satisfactory. The most recent identification of soma as *Amanita muscaria* appears, from the indirect evidence at hand, to be highly probable.

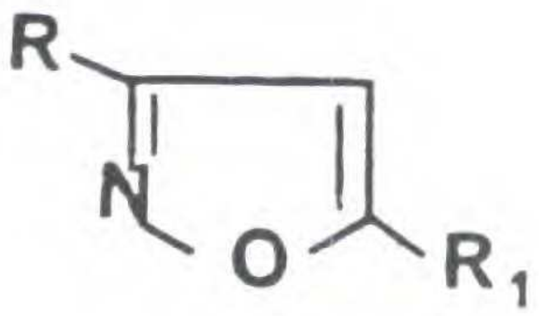
In the 18th Century, Europeans discovered the narcotic use of *Amanita muscaria* among primitive tribesmen of Siberia. Until very recently, it was employed as an orgiastic or shamanistic inebriant by the Ostyak and Vogul, Finno-Ugrian peoples in western Siberia, and the Chukchi, Koryak and Kamchadal of northeastern Siberia. Tradition has established its use amongst other peoples (Wasson 1967, 1968).

In Siberia, several mushrooms sufficed to induce intoxication—taken as extracts in water or milk, alone or with the juice of *Vaccinium uliginosum* L. or *Epilobium angustifolium* L. A dried mushroom may be held moistened in the mouth, or women may chew the mushrooms and roll them into pellets for the men to ingest. Since the mushrooms often were expensive, the Siberians practiced ritualistic drinking of the urine of an intoxicated person, having discovered that the inebriating principles were excreted unaltered by the kidneys. Urine-drinking is mentioned in the Rig Veda hymns to *soma* (Wasson 1968).

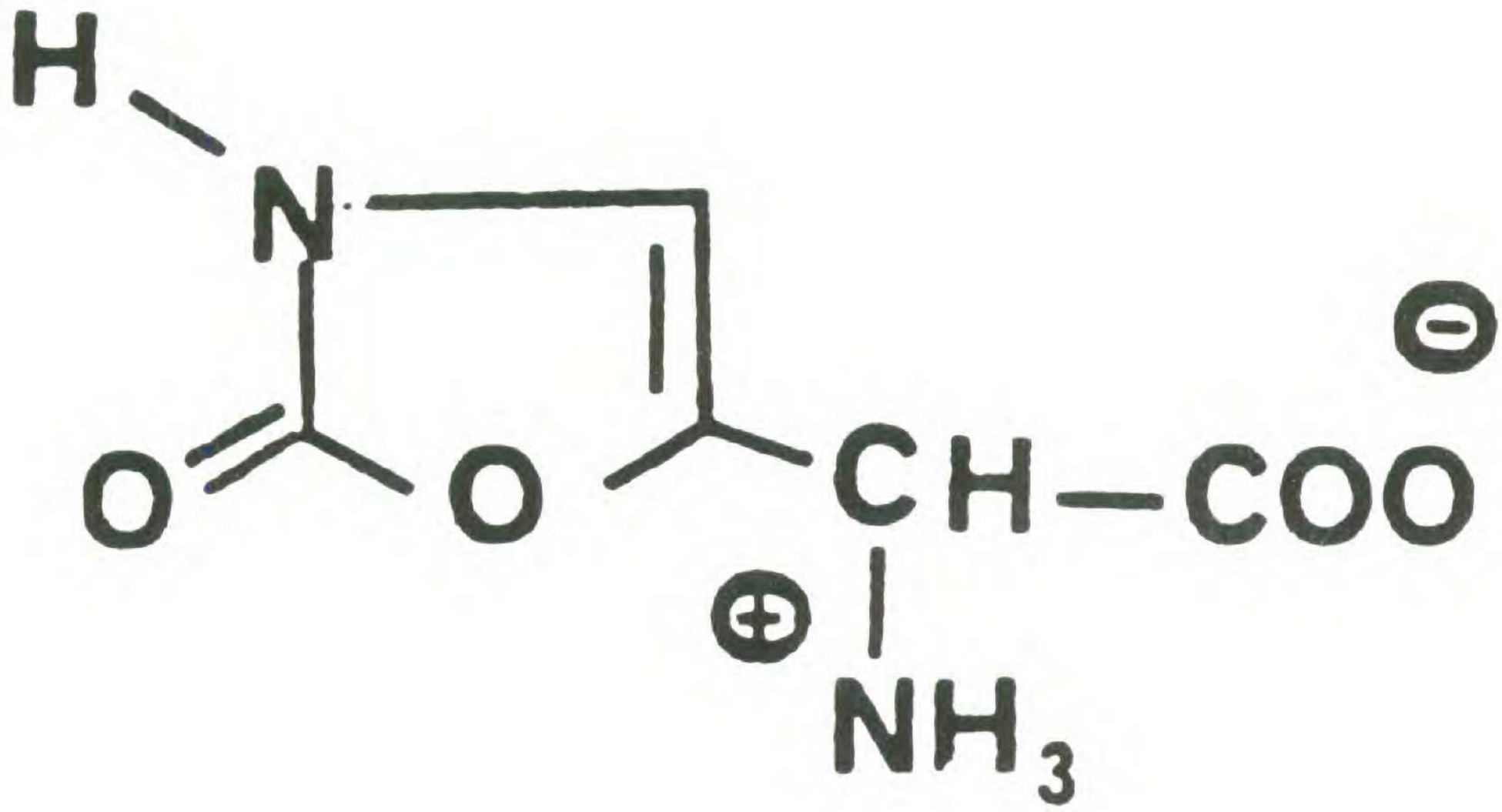
There is indirect evidence suggesting that *Amanita muscaria* may have been used in Middle America. The ceremonial use of the fly agaric has been recently discovered amongst the Ojibway Indians of the United States (Wasson, pers. commun.), and unconfirmed indications of its use in northwestern Canada have recently been indicated (Halifax, pers. comm.).

Since the discovery in 1869 of muscarine, the intoxicating activity of *Amanita muscaria* has been attributed to this alkaloid. Recent studies, however, have indicated that muscarine represents a very minor constituent of the mushroom to which the strong inebriation could hardly be attributed. Trace amounts of bufotenine in the carpophores, likewise. could not be responsible, if indeed it be present. The reported presence of tropane alkaloids has been shown to be due to incorrect interpretation of chromatographic data. Other compounds detected in *A. muscaria* are choline, acetylcholine and muscaridine (Eugster 1965; Wasser 1967; Wasson 1967).

Recent chemical and pharmacological studies have shown that the principal biologically active constituents appear to be muscimol (XVI), the enolbetaine of 5-aminoethyl-3-hydroxyisoxazole—an unsaturated cyclic hydroxamic acid which is excreted in the urine; and ibotenic acid (XVII), the zwitterion of α-amino-α-3-hydroxyisoxazolyl-5-acetic acid monohydrate. The less active muscazone (XVIII), likewise an amino acid [α-amino-α-2(3H)-oxazolonyl-5-acetic acid] is present in varying but lesser amounts. Structurally related to these isoxazoles is the antibiotic oxamycin, which often has psychoactive side effects in man: mental confusion, psychotic depression, abnormal behavior. Other active substances, still not structurally elucidated, are also known to be present (Eugster 1967; Hatfield et al. 1975; Wasser 1967).



	R	R_1
XVI	$-O^-$	$-CH_2-NH_3^+$
XVII	$-OH$	$-CH(COO^-)(^+NH_3)$



XVIII

Widely recognized variability in the psychoactivity of *Amanita muscaria* results probably from varying ratios of ibotenic acid and muscimol in the carpophores. In spite of appreciable variability between individuals, certain effects are characteristic: twitching of the limbs, a period of good humour and euphoria, macropsia, occasionally colored visions of the supernatural and illusions of grandeur. Religious overtones frequently occur, and the user may become violent, dashing madly about, until exhaustion and deep sleep overtake him.

In a recent interesting account, Ott has described in some detail the current social use of Amanitas in the United States (Ott 1978).

The genus *Amanita,* comprising from 50 to 60 species, is cosmopolitan, occurring on all continents except South America and Australia, but the species occupy definitive areas. *Amanita muscaria* has recently been found growing in large colonies near Medellín, Colombia, but it appears to have been introduced, perhaps with pines for reforestation. A number of the species are toxic, and their chemical constitution, still poorly understood, seems to be variable.

5. β-PHENYLETHYLAMINES

Cactaceae

Lophophora Coult.

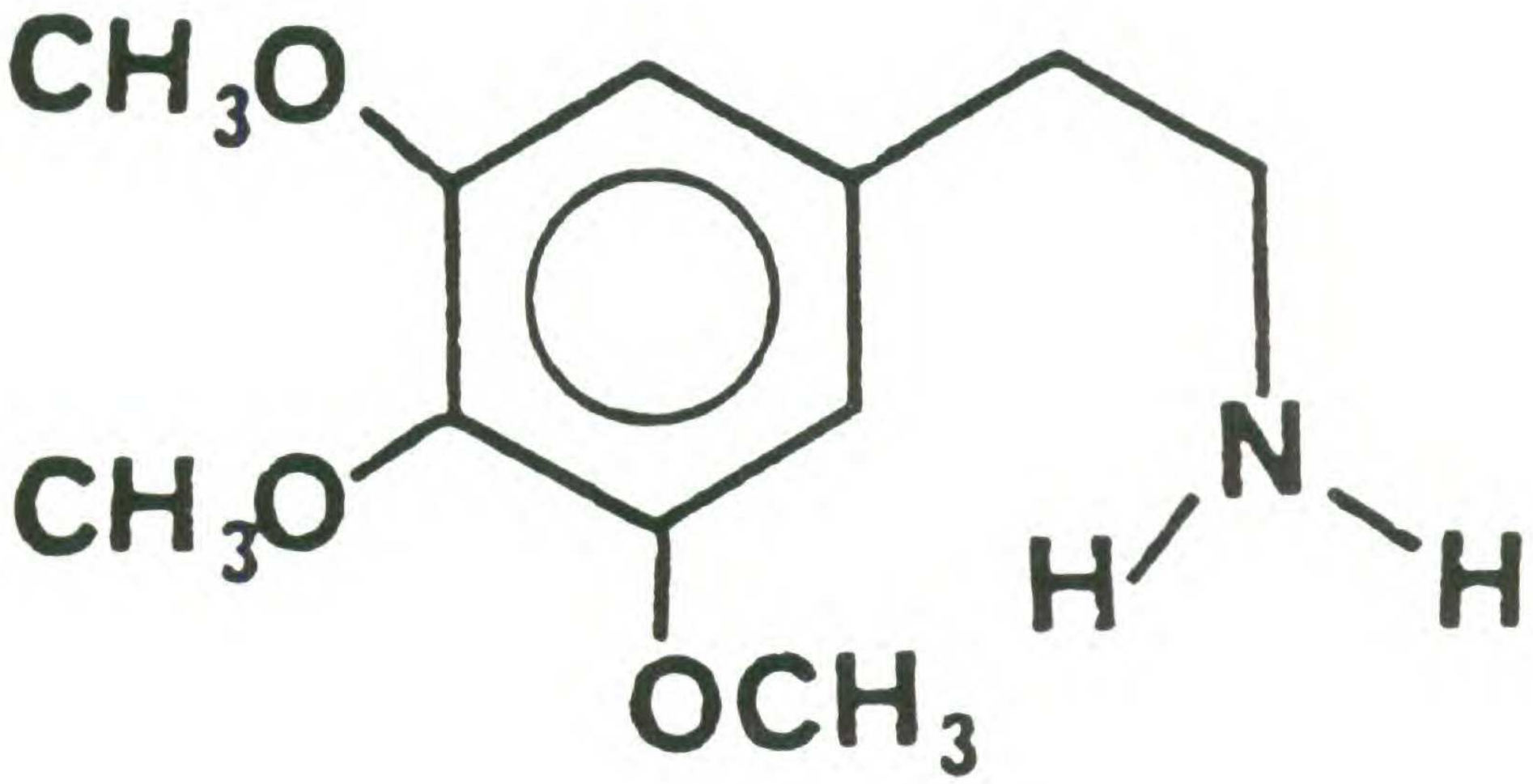
One of the ancient sacred hallucinogens of Mexico, still in use, is the small, grey-green, napiform, spineless cactus *peyote: Lophophora Williamsii* (Lem.) Coult. It might well be called the "prototype" of hallucinogens, since it has been one of the most spectacular and most thoroughly studied psychotomimetics known. It was first fully described by the early Spanish medical doctor Francisco Hernandez, but many other colonial Spanish chroniclers detailed the strange story of peyote. Peyote rites persist in several tribes of northern Mexico. It was used in Texas in 1760, was known amongst American Indians during the Civil War but came to public attention in the United States about 1880, when the Kiowas and Comanches elaborated a typical Plains Indian vision-quest ritual around its ceremonial ingestion. The Peyote Cult, organized as the Native American Church, has gradually spread to many tribes in the United States and Canada and counts at least 250,000 adherents (Collier 1952; LaBarre 1959, 1960; Schultes 1937a, 1937b and 1937c). The chlorophyll-bearing crown of the cactus is eaten. It can be dried into discoidal "mescal buttons", which are virtually indestructible and can be shipped over long distances.

The peyote cactus was first botanically described as *Echinocactus Williamsii* Lem. in 1845. In the chemical literature, it is still frequently referred to this genus and to *Anhalonium* Lem. In 1894, it was placed in the genus *Lophophora*. Its nomenclature and taxonomy are still confused, and *L. Williamsii* has more than 25 synonyms, most of them referring to age-forms of the variable crown (Anderson 1980; Schultes 1937a). *Lophophora* was once accepted as monotypic. Recent work, however, indicates that *L. diffusa* (Croiz.) Bravo of Querétaro, Mexico, is morphologically and chemically worthy of specific recognition (Bruhn 1975b, 1976).

Lophophora is placed in the tribe *Cereae,* subtribe *Echinocactanae,* a subtribe of some 28 genera, many of them small or monotypic and included in *Echinocactus* Link, (*Ariocarpus* Scheidw., *Astrophytum* Lem., *Roseocactus* Berger, etc.). It

occurs in central Mexico and near the Rio Grande in southern Texas.

More than 30 alkaloids and their amine derivatives have been isolated from *Lophophora Williamsii,* belonging mainly to the β-phenylethylamines and the biogenetically related simple isoquinolines (Kapadia and Fayez 1970). The β-phenylethylamine mescaline (XIX) is exclusively responsible for the visual hallucinations; its derivatives, N-methylmescaline and N-acetylmescaline, are apparently not active. Hordenine, another β-phenylethylamine, is also present in peyote. Peyonine, a novel β-phenylethylpyrrole, was recently isolated from this cactus, pharmacology of this derivative of mescaline, or its precursors, has not yet been reported (Agurell 1969; Reti 1950). Mescaline has been reported in *Lophophora diffusa* (Bruhn and Holmstedt 1974).



XIX

Ariocarpus Scheidw.

N-methyltyramine, 3,4-dimethoxy-N-methylphenylethylamine and 3,4-dimethoxy-N,N-dimethylphenylethylamine, are reported in *Ariocarpus scapharostrus* Boedeker (Bruhn 1975a). Several species of *Ariocarpus*—*A. fissuratus* (Engelm.) Schum. and *A. retusus* Scheidw.—are known as false peyotes and may oc-

casionally be employed in northern Mexico in magic and witchcraft (Schultes and Hofmann 1973, 1979 and 1980).

Opuntia Mill.

Opuntia cylindrica (Lam.) DC. contains 0.9 percent mescaline (Turner and Heyman 1960) and *O. spinosior* (Engelm.) Toumey contains 0.00004% of the same alkaloid (Kruger et al. 1977; Pardanani et al. 1978).

Pelecyphora Ehrenb.

The Mexican cactus *Pelecyphora aselliformis* Ehrenb. is reported to contain mescaline (Díaz 1977, 1979).

Trichocereus (Berger) Riccob.

Several species of the South American genus *Trichocereus* have yielded mescaline: *T. macrogonus* (Salm-Dyek) Riccob. *T. Pachanoi* Britton & Rose, *T. Terscheckii* (Parment.) Britt. & Rose, *T. Werdermannianus* Backeb. (Agurell 1969; Vanderveen et al. 1974); and *T. peruvianus* Britt. & Rose (Pardanani et al. 1977). The large columnar *T. Pachanoi* of the dry Andes--called *San Pedro* in Peru and *aguacolla* in Ecuador—is employed in magic and folk medicine in northern Peru (Poisson 1960). Together with another cactus, *Neoraimondia macrostibas* (Schum.) Britton & Rose, and *Isotoma longiflora* Presl, *Pedilanthus tithymaloides* Poit. and a species of *Brugmansia,* it is the base of an hallucinogenic drink called *cimora* (Schultes 1970c).

There are some 40 species of *Trichocereus* known from subtropical and temperate South America.

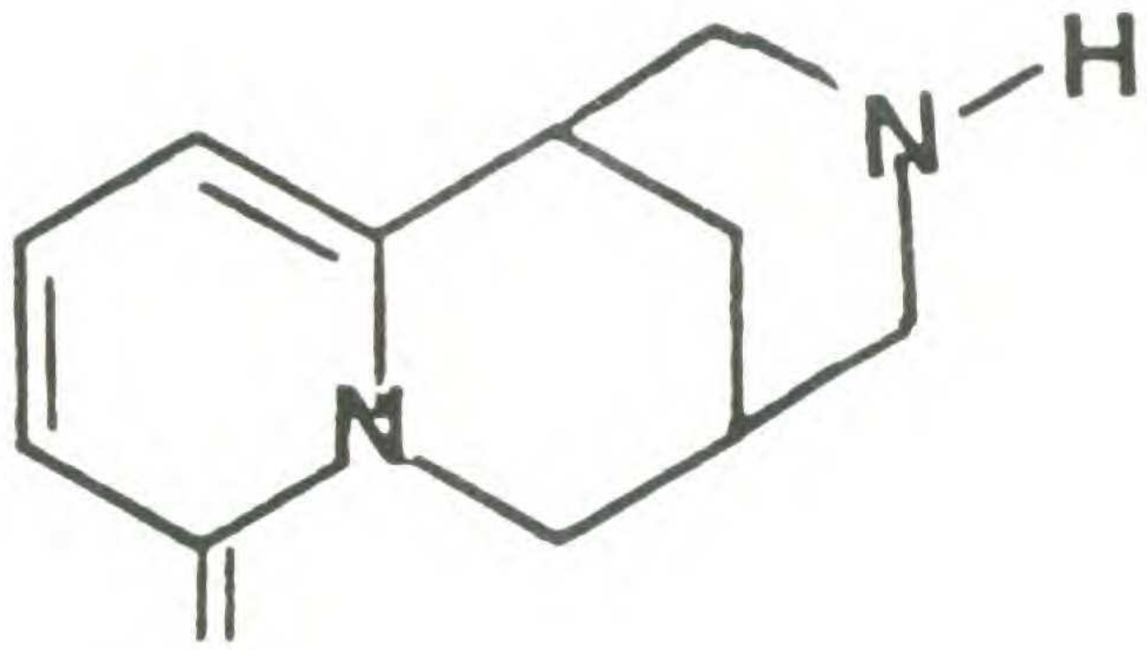
6. QUINOLIZIDINES

Leguminosae

Cytisus L.

The hallucinogenic use by Yaqui medicine men in northern Mexico of *Cytisus (Genista) canariensis* (L.) O.Ktze., a shrub native to the Canary Islands, not to Mexico, has been documented (Fadiman 1965). It is rich in the alkaloid cytisine (ulexine, baptitoxine, sophorine) (XX) which occurs commonly in the Leguminosae (Willaman and Schubert 1961).

About 25 species of *Cytisus.* native to the Atlantic Islands, Europe, and the Mediterranean area, are known, and a number of the species are toxic.



XX

Sophora L.

A shrub of dry areas of the American Southwest and adjacent Mexico, *Sophora secundiflora* (Ort.) Lag. ex DC. yields the so-called *mescal beans* or *red beans.* Mexican and Texan Indians formerly employed these beans in the ceremonial Red Bean Dance as an oracular and divinatory medium and for visions in initiation rites (LaBarre 1959; Schultes 1937a). Its use died out in the United States with the arrival of peyote, a much safer hallucinogen. Mescal beans, which contain cytisine, (Izaddoost 1975; Keller 1975), are capable of causing death by asphyxiation (Howard 1957). The pharmacology of cytisine has been reported (Zachowski 1938). Historical reports of the mescal bean go back to 1539, but archaeological remains suggest their ritualistic use earlier than 1000 A.D. (Adovasio and Fry 1976; Campbell 1958).

Sophora, with some 50 species, occurs in tropical and warm temperate parts of both hemispheres.

Lythraceae

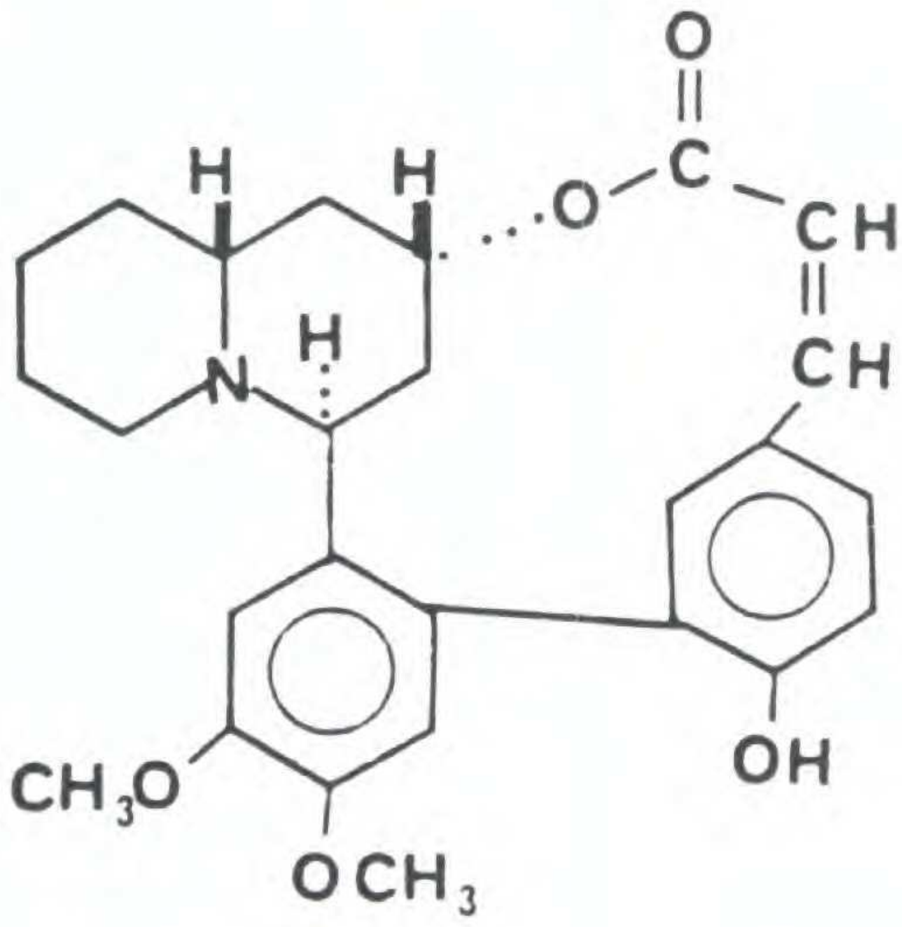
Heimia Link & Otto

Heimia salicifolia (HBK.) Link & Otto has been valued in Mexican folk medicine since early times. Known as *sinicuichi,* its leaves are wilted, crushed in water, and the juice set in the sun to ferment. The resulting drink is mildly intoxicating. Usually devoid of unpleasant after effects, it induces euphoria characterized by drowsiness, a sense of shrinkage of the surroundings,

auditory hallucinations and a general removal from a sense of reality (Robichaud et al. 1964, 1965).

Alkaloids were first reported from *Heimia salicifolia* in 1964; the major psychoactive one appears to be cryogenine (vertine) (XXI) (Blomster et al. 1964; Douglas et al. 1964; Kaplan and Malone 1966; Robichaud et al. 1964, 1965). Differing from the usual quinolizidines in having the quinolizidine as part of a larger system of rings, cryogenine has been found only in the Lythraceae.

The genus *Heimia* comprises three hardly distinguishable species and ranges from southern United States to Argentina.



XXI

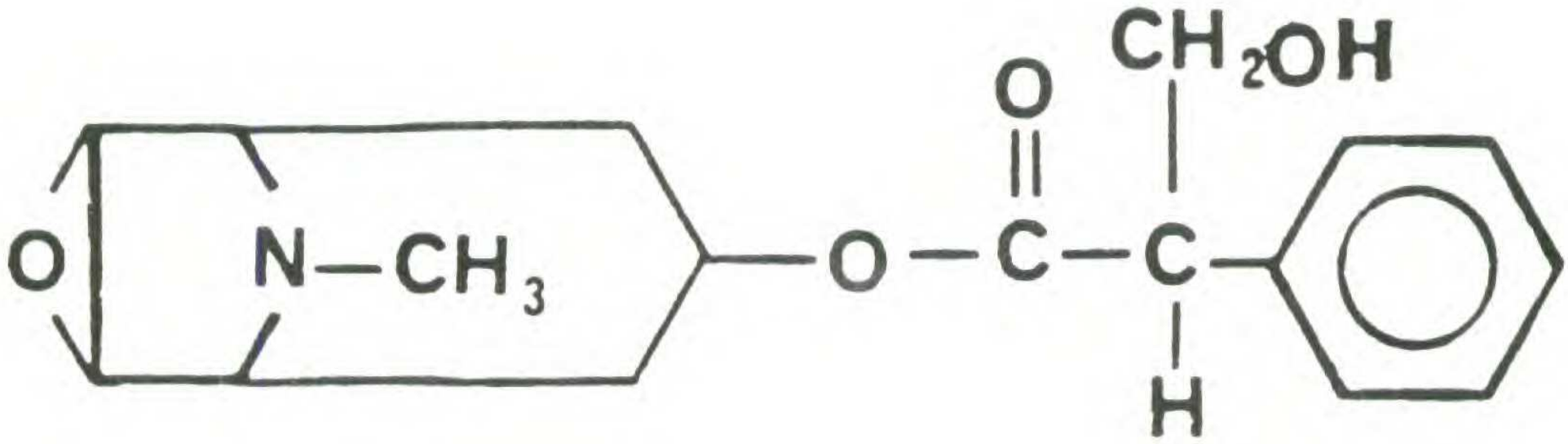
7. TROPANES

Solanaceae

Atropa L.

The *belladonna* or *deadly nightshade,* (*Atropa Belladonna* L.) was utilized as an hallucinogen in Europe in medieval witches' brews. Its principal active constituent has long been known to be scopolamine (XXII); additional minor tropane alkaloids are also present (Wagner 1969).

There are four species of *Atropa,* distributed in Europe, the Mediterranean area, and from Central Asia to the Himalayas.



XXII

Brugmansia Pers.

Usually considered to represent a subgenus or section of *Datura* L., *Brugmansia* has recently been shown conclusively on biological as well as morphological characters to deserve distinction as a genus (Lockwood 1973). Native to South America, the nine species are arborescent. All appear to be cultigens unknown in the truly wild state (Lockwood 1979).

The most widespread species, *Brugmansia aurea* Lagerh., occurs throughout the Andes from Colombia to northern Chile at elevations of 8,000 to 10,000 feet. Another striking species, *B. sanguinea* (R. & P.) D. Don is native from Colombia to Peru. Most of the species were of the greatest social and religious importance in ancient Andean cultures (Lockwood 1979). The Chibchas of Colombia, for example, administered potions of *B. aurea* to wives and slaves of deceased chieftains to induce a stupour prior to their being buried alive with the departed master. *B. sanguinea* was a sacred ceremonial plant in the Temple of the Sun in Sogamosa, in northern Colombia, where its psychoactive properties must have had a role in religious rites.

Modern Indians of Colombia, Ecuador and Peru still use species of *Brugmansia* in magico-religious and medicinal rites. The Mapuche of Chile use it as correctional medicine for recalcitrant children, believing that the spirit of ancestors admonish the youths through the hallucinations. In modern Peru, Indians still believe that *B. sanguinea* permits them to communicate with ancestors and that, through visual hallucinations, it can reveal treasures preserved in graves or "huacas"—the reason for its local name *huacacachu* ("grave plant").

The drug is most commonly taken in the form of powdered seeds added to fermented drinks or as a tea of the leaves. A dangerous hallucinogen, *Brugmansia* brings on an intoxication often so violent that physical restraint is necessary before the onset of a deep stupor, during which the visions are experienced.

The species currently recognized are *Brugmansia arborea,* (L.) Lagerh., *B. aurea, B.* x *candida* Pers., B. x *dolichocarpa* Lagerh., *B.* x *insignis* (B. Rodr) Lockwood, *B. sanguinea,* B. *suaveolens* (H. & B. ex Willd.) Bercht. & Presl, *B. versicolor* Lagerh. and *B. vulcanicola* (A.S. Barclay) R.E. Schult. (Schultes and Hofman, 1980).

The most intensive use of *Brugmansia* appears to be in Sibundoy in southern Colombia, where Kamsá and Ingano medicine men preserve, through vegetative reproduction, highly atrophied clones for which they have native names. These monstrosities — possibly mutants induced by viral infection — vary in narcotic strength and are, consequently, used for different purposes (Bristol 1966, 1969; Lockwood 1973; Schultes and Hofmann 1979b).

What may possibly represent an extreme variant of an indeterminate species of *Brugmansia* has been described as a distinct genus: *Methysticodendron* R.E. Schult. Native to the high, isolated Valley of Sibundoy, *M. Amesianum* R.E. Schult. is important amongst the Kamsá and Ingano as an hallucinogen and medicine, where it is called *culebra borrachera* ("intoxicant of the snake") (Schultes, 1955).

The chemical constitution of *Brugmansia* is similar to that of *Datura,* with tropane alkaloids the active principles. In *B. aurea* from the Andes, scopolamine constitutes from 50-60% of the total alkaloid content, as contrasted with 30-34% for the same plant grown in England and Hawaii. Aerial portions of *B. aurea,* originally from the Colombian Andes, but cultivated in England, contain scopolamine, norscopolamine, atropine, meteloidine and noratropine; roots have the same alkaloids, as well as 3α6β-ditigloyloxytropane-7β-ol, 3α-tigloyloxytropane and tropine. Leaves of the same stock grown in Hawaii contain the identical spectrum of alkaloids but vary in total content and amount of scopolamine (Bristol et al. 1969). The leaves and stems of *Methysticodendron Amesianum* contain scopolamine,

up to 80% of the total alkaloid content (Pachter and Hopkinson 1960).

Significantly, the alkaloid content in the Sibundoy cultivars of *Brugmansia aurea* correlate closely with reports of their relative toxicity by the Indians of Sibundoy. Notwithstanding the great age of their hallucinogenic and medicinal usage, Brugmansias are still the subject of much botanical, ethnobotanical and phytochemical interest.

Datura L.

Datura has a long history an an hallucinogenic genus in both hemispheres (Hoffman 1968; Lewin 1927; Safford 1920, 1921; Schultes; Schultes and Hofmann 1979). The most intense use and the greatest concentration of species occurs in the American Southwest and adjacent Mexico, where four closely related species are known: *D. inoxia* Mill. (more commonly known as *D. meteloides* DC.), *D. pruinosa* Greenm., *D. quercifolia* HBK. and *D. Wrightii* Regel. *Datura Stramonium* L. is now generally believed to be of New World origin and appears to be the species formerly employed by the natives of eastern North America.

There exists in Mexico an anomalous aquatic species, *Datura ceratocaula* Ort. which is so distinct that it is accommodated in a separate section of the genus. It was one of the most sacred hallucinogens of the Aztecs, who knew it as "sister of ololiuqui" (*ololiuqui* = the highly sacred morning glory, *Turbina corymbosa*). Modern Mexican Indians still revere it and call it *torna-loco* ("maddening plant") (Schultes and Hofmann 1973). The most commonly employed species is *D. inoxia,* known today in Mexico as *toloache;* by the Aztecs as *toloatzín.* Many tribes in Mexico and the Southwest still value it as a magic plant. The Zuni use it as an hallucinogen and analgesic; the plant belongs to the rain priests who alone may collect it. They commune at night with the feathered kingdom to intercede with the gods for rain, putting the powdered root into the eyes. The Yuman take it to induce dreams and gain occult powers and predict the future. Yokut boys, at initiation, take it once in a lifetime, but youths studying to be shamans must use it once a year. The Tarahumara add *D. inoxia* to tesguino, a fermented magic drink, to make it stronger; they also take a drink prepared

from the seeds and leaves ceremonially to induce visions. Amongst some Mexican Indians, *toloache* is considered an hallucinogen inhabited, unlike peyote, by a malevolent spirit (Hoffman, 1968).

In the Old World, *Datura* never was used so ceremonially as in the New World. The most important species in the Eastern Hemisphere is *D. Metel* L. mentioned as a drug called *jouzma-thel* in the 11th Century by the Arabian physician Avicenna. In China, it was considered sacred: when Buddha preached, heaven sprinkled the plant with drops of dew or rain. Today, *Datura* seeds are frequently mixed with tobacco or *Cannabis* to be smoked. A less important Old World species, *D. ferox* L., is widely employed in parts of Africa (Safford 1920, 1921).

The active principles of all species of *Datura* are tropane alkaloids. They vary in relative concentrations from species to species. *D. Stramonium* seeds, for example, contain about 0.4% of alkaloid, consisting mainly of hyoscyamine with a small amount of scopolamine and minute amounts of atropine (Claus and Tyler 1967). In *D. Metel,* the following total alkaloids are reported: in fruits, 0.12%; leaves 0.2–0.5%; roots 0.1–0.2%; seeds 0.2–0.5%; the main component is scopolamine, with the minor alkaloids meteloidine, hyoscyamine, norhyoscyamine, norscopolamine, as well as two alkaloids not belonging to the tropane group—cuscohygrine and nicotine (Schultes and Hofmann 1973).

Hyoscyamus L.

Henbane, a toxic species of the genus, is *Hyoscyamus niger* L. and was once widely cultivated in Europe as a narcotic. It entered medieval witches' brews as an hallucinogenic ingredient (Schultes and Hofmann 1979). The psychoactive effects of henbane are attributed mainly to scopolamine (Wagner 1969).

Hyoscyamus comprises about 20 species of Europe, northern Africa and southwestern and central Asia.

Latua Phil.

A century ago, a spiny shrub of Chile, now known botanically as *Latua pubiflora* (Griseb.) Baill., the only member of an endemic genus, was identified as a virulent poison, inducing delirium and visual hallucinations. It was employed by local

Indians, who knew the shrub as *latué* or *arbol de los brujos,* to cause permanent insanity (Murillo 1889). Recent phytochemical studies indicate the presence of atropine and scopolamine (Bodendorf and Kummer 1962; Plowman et al. 1971; Silva and Mancinelli 1959; Schultes 1979).

Mandragora L.

The famed mandrake of Europe, *Mandragora officinarum* L., owes the fame that it has acquired mainly to its hallucinogenic toxicity. The active principles are tropane alkaloids, primarily hyoscyamine, scopolamine, and mandragorine (Staud 1962; Schultes and Hofmann 1979; Wagner 1969).

Six species of *Mandragora* are known, native to the region from the Mediterranean to the Himalayas.

Solandra Sw.

In parts of Mexico, several species of the solanaceous *Solandra—S. guerrenensis* Martínez and S. *brevicalyx* Standl.—are employed as sacred hallucinogens. The Aztec names of the former species are *hueipatl* and *tecomaxochitl;* amongst the Huichols, the latter is known as *kieli* and represents a god-plant (Knab 1977). A tea is made from the juice of the branches.

Much remains to be done before the chemistry of *Solandra* is fully understood. Small amounts of atropine, noratropine, (—)-hyoscyamine and norhyoscyamine (Raffauf 1970) as well as tropine, nortropine, cuscohygrine and other bases (Evans et al. 1972) are found.

It is possible that *Solandra guttata* D. Don and *S. nitida* Zucc. are similarly used in Mexico (Schultes and Hofmann 1980).

Solandra is a genus of about 10 species native to Mexico and tropical America. It is closely allied to *Datura* and *Brugmansia.*

8. TRYPTAMINES

Acanthaceae

Justicia L.

The Waikas of the Orinoco headwaters in Venezuela and in northwestern Brazil, occasionally dry and pulverize the leaves of *Justicia pectoralis* Jacq. var. *stenophylla* Leonard as an admixture to their *Virola*-snuff (Carias-Brewer and Steyermark 1976; Schultes 1967; and Schultes and Holmstedt 1968).

There are suspicions that this aromatic herb may contain tryptamines (Holmstedt, pers. comm.) and the plant may on occasion be the basis, without admixtures, of an hallucinogenic snuff (Chagnon et al. 1971). If the preliminary indications can be verified, it will for the first time establish the presence of these indoles in the Acanthaceae.

There are more than 300 species of *Justicia* in the tropical and subtropical parts of both hemispheres.

Agaricaceae

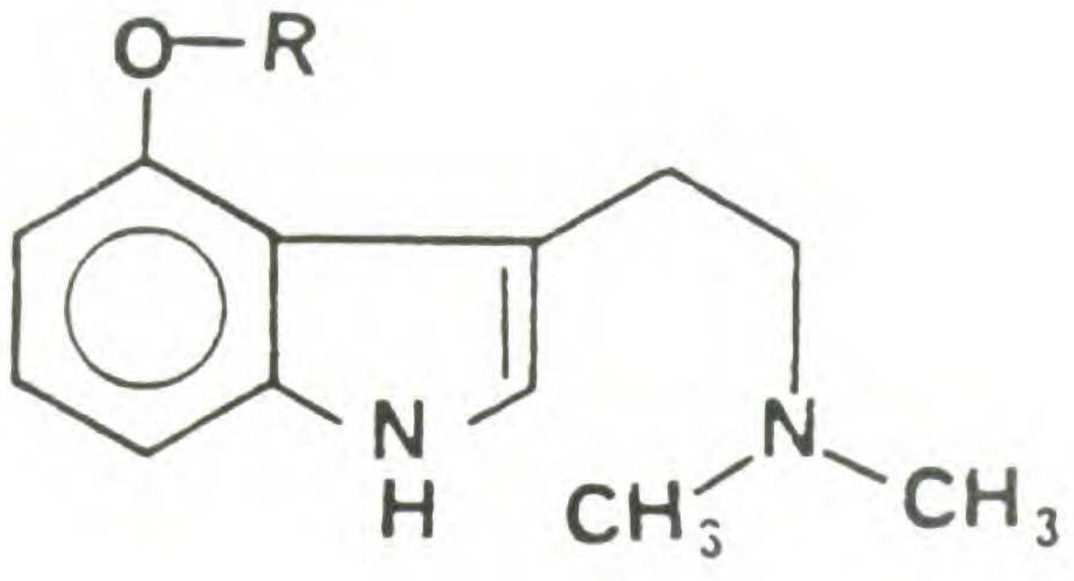
Conocybe, Fayod; *Panaeolus,* (Fr.) Quélet; *Psilocybe* (Fr.) Quélet; and *Stropharia* (Fr.) Quélet

The Spanish conquerors found Mexican Indians practicing religious rites in which mushrooms were ingested as a sacrament, permitting them to commune through hallucinations with the spirit world. The Aztecs knew these "sacred" mushrooms as *teonanacatl* ("food of the gods") (Heim and Wasson 1959; La Barre 1959; Ott and Bigwood 1978; Safford 1915; Schultes 1939).

Persecution by the Roman church drove the cult into hiding in the hinterlands. Notwithstanding many descriptions in the writings of the early chroniclers, no evidence that the narcotic use of mushrooms had persisted was uncovered until about 40 years ago. Botanists had even postulated that *teonanacatl* might be the same plant as peyote: that the discoidal crown of the cactus, when dried, superficially resembled a dried mushroom and that the earlier writers had confused the two or had been deliberately duped by their Aztec informants (Safford 1916b). Then, in the late 1930s, several investigators found an active mushroom cult amongst the Mazatecs in Oaxaca and collected, as the hallucinogenic fungi, *Panaeolus sphinctrinus* (Fr.) Quél. and *Stropharia cubensis* Earle. More intensive work during the 1950's brought to over 24 species, in at least four genera, the number of basidiomycetes employed currently in six or more tribes of Mexican Indians (Guzmán 1959; Heim 1956a, 1956b, 1957a, 1957b, 1963a; Schultes 1939; Schultes and Hofmann 1973; Singer 1958; Wasson 1958; Wasson and Wasson 1957; Ott and Bigwood 1978).

It now appears that the mushroom cults are of great age and were once much more widespread. Archeological artefacts, now called "mushroom stones," excavated in great numbers from highland Mayan sites in Guatemala, are dated conservatively at 1000 B.C. Consisting of a stem with a human or animal face and crowned with an umbrella-like top, these icons indicate the existence of a sophisticated mushroom cult at least 3000 years ago (Schultes and Hofmann 1979).

Perhaps the most important species employed in Mexican mushroom rites are *Psilocybe aztecorum* Heim, *P. caerulescens, P. mexicana* Heim, *P. zapotecorum* Heim, and *Stropharia cubensis* (Heim and Wasson 1959; Heim 1967). All of these have been found to contain a most extraordinarily psychoactive compound, psilocybin (XXIII)—an hydroxyindole alkylamine with a phosphorylic ester group: 4-phosphoryloxy-N,N-dimethyltryptamine, and sometimes the unstable derivative, psilocin (XXIV): 4-hydroxy-N,N-dimethyltryptamine. Psilocybin is the only indole compound known from the Plant Kingdom with a phosphoric acid radical and both psilocybin and psilocin are novel among indoles in having the hydroxy radical substituted in the 4-position (Schultes 1976a; Schultes and Hofmann 1979). Tryptophan is probably the biogenetic precursor of psilocybin (Hofmann et al. 1958, 1959; Hofmann and Troxier 1959; Hofmann and Tscherter 1960).



	R
XXIII	PO_3H^-
XXIV	H

The hallucinogenic activity of psilocin and psilocybin has been reported and reviewed (Cerletti 1959; Isbell 1959; and Weidmann et al. 1958).

These two indoles may occur widely in *Psilocybe* and related genera.

One or both have been isolated from a large number of mushrooms from North and South America, Europe and Asia: from numerous species of Psilocybe (Repke et al. 1977a; Ott and Guzmán 1976; Semerdzieva and Nerud 1973); from Concoybe (Repke et al. 1977a); from Copelandia (Benedict et al 1962, 1967); from six species of Gymnopilus (Hatfield et al. 1978); from Psathyrella (Ott and Guzmán 1976); and from several species of Panaeolus (Repke et al. 1977a; Rubbers et al. 1969).

The occurrence of 4-substituted tryptamines (psilocybin or psilocin) has been reported from *Panaeolus sphinctrinus,* and this psychoactive mushroom also contains 5-hydroxytryptamine and 5-hydroxytryptophan; the closely related *Panaeolus campanulatus* apparently does not contain the hallucinogenic constituents (Tyler and Malone 1960).

Early missionaries in Amazonian Peru reported that the Yurimagua Indians employed an intoxicating beverage made from a "tree fungus" (Schultes 1966a). Although no modern evidence points to the use of an hallucinogenic fungus in that area, *Psilocybe yungensis* Singer & Smith has been suggested as a possible identification of the mushroom (Schultes 1966a).

Although psilocybin-containing mushrooms have been collected in South America, there is no evidence that they are employed as sacred inebriants today. It has been suggested that certain anthropomorphic archaeological gold pectorals with mushroom-like domes found in Colombia and dated from 1000 to 1500 A.D. may indicate the former use of shamanic ceremonies of intoxicating mushrooms. Psilocybin-containing mushrooms have been found in Colombia (Schultes and Bright 1979).

The principal genera of hallucinogenic mushrooms of Mexico are small but widespread: *Conocybe* is cosmopolitan; *Panaeolus* is cosmopolitan, occurring primarily in Europe, North America, Central America, and temperate Asia; *Psilocybe,* almost cosmopolitan, is distributed in North America, South America, and

Asia; and *Stropharia,* likewise almost cosmopolitan, ranges through North America, the West Indies and Europe.

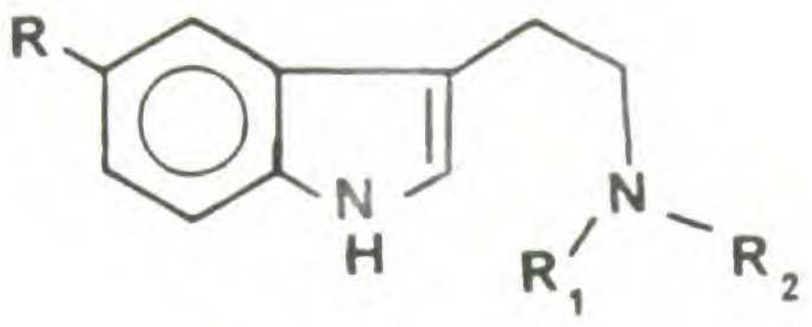
Leguminosae

Anadenanthera Speg.

The New World snuff prepared from beans of *Anadenanthera (Piptadenia) peregrina* (L.) Speg., is known in the Orinoco basin of Colombia and Venezuela, centre of its present use, as *yopo.* It represents probably the cohoba encountered in Hispaniola by Columbus' second voyage in 1496 (Safford 1916a). Von Humboldt, Spruce and other explorers who mentioned it were all astonished by its hallucinogenic potency.

The beans of this medium-sized tree, usually roasted, are crushed and mixed with ashes or calcined shells. The powder is ceremonially blown into the nostrils through bamboo tubes or snuffed individually through bird bone tubes (Carias-Brewer et al. 1976). The intoxication is marked by fury, followed by an hallucinogenic trance and eventual stupour (Granier-Doyeux 1965).

Five indoles have been isolated from *Anadenanthera peregrina,* chief of which are N,N-dimethyltryptamine (XXV) and bufotenine (5-hydroxy-N,N,-dimethyltryptamine) (XXVI) (Fish et al. 1955; and Schultes 1970c, 1976a). Other indoles found in this species are 5-methoxy-N,N,-dimethyltryptamine (XXVII), N_b-methyltryptamine (XXVIII) and 5-methoxy-N_b-methyltryptamine (XXIX).



	R	R_1	R_2
XXV	H	CH_3	CH_3
XXVI	HO	CH_3	CH_3
XXVII	CH_3	CH_3	CH_3
XXVIII	H	H	CH_3
XXIX	CH_3O	H	CH_3

Indirect evidence has suggested that another species, *Anadenanthera colubrina* (Vell.) Brenan, might formerly have been the source of the narcotic snuffs known in southern Peru and Bolivia as *vilca* or *huilca,* and in Argentina as *cebil* (Altschul 1964). Since this species is closely related to the more northern *A. peregrina,* and its chemical constituents are very similar, *A. colubrina* may well have been aboriginally of value as a hallucinogen. Field work has established its contemporary use as a narcotic in northern Argentina (Califano 1975).

Anadenanthera comprises only the two species discussed above. Native to South America, they are distinguished from the closely allied genus *Piptadenia* both morphologically and chemically (Altschul 1964).

Mimosa L.

The allied genus *Mimosa* likewise yields a psychotomimetic, *vinho de jurema.* An infusion of the roots of *M. hostilis* (Mart.) Benth. forms the centre of the ancient Yurema cult of the Kariri, Pankarurú, and other Indians of Pernambuco State, Brazil (Schultes 1965, 1966a). The drink, said to induce glorious visions of the spirit world, was reported to contain an alkaloid originally called nigerine; now known to be N,N-dimethyltryptamine (XXV), the active principle (Gonçalves de Lima 1946).

The genus *Mimosa* comprises about 500 tropical or subtropical herbs and small shrubs, mostly American, but a few are native to Africa and Asia. It is closely related to *Anadenanthera* and *Piptadenia.*

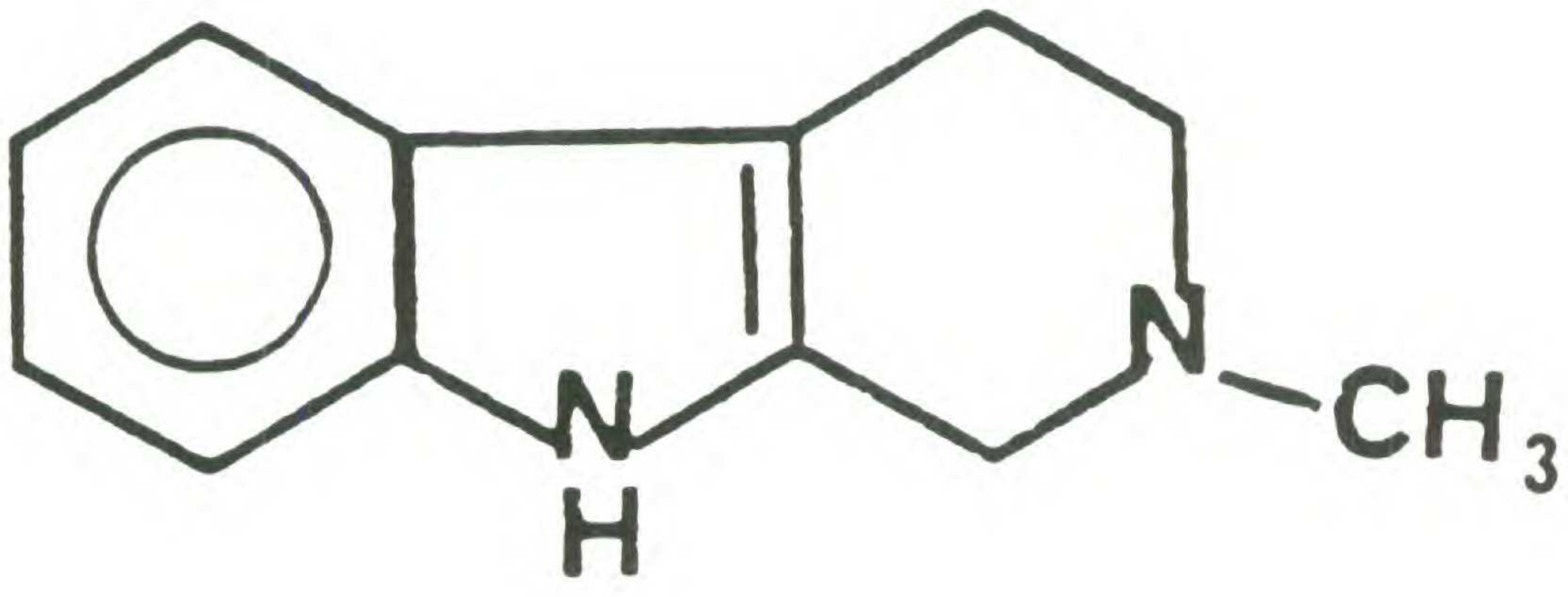
Malpighiaceae

Diplopterys A. Juss.

One of the numerous admixtures of the *ayahuasca-caapi-yajé* drink prepared from bark of *Banisteriopsis Caapi* or *B. inebrians* (which contain β-carboline bases) is the leaf of *Diplopterys Cabrerana*,* known in the western Amazon of Colombia and

*The correct name of this plant has recently been shown to be *Diplopterys Cabrerana* (Cuatr.) Gates (Gates 1979). All the chemical studies, however, have been published under *Banisteriopsis Rusbyana* (Ndz.) Mort.

Ecuador as *oco-yajé*. The natives add the leaf to heighten and lengthen visions. Recent examinations indicate that *D. Cabrerana* has in its leaves and stems N,N-dimethyltryptamine and traces of two other narcotically utilized compounds, N,N-dimethyltryptamine and traces of other tryptamines (N_b-methyltryptamine; 5-methoxy-N,N-dimethyltryptamine; and N_b-methyltetrahydro-β-carboline (XXX) (Agurell et al. 1968a and b; Der Marderosian et al. 1968; Poisson 1965). Tryptamines have apparently not hitherto been reported from the Malpighiaceae.



XXX

Myristicaceae
Virola Aubl.

Hallucinogenic snuffs are prepared in northwestern Brazil and adjacent Colombia and Venezuela from the reddish bark "resin" of trees of *Virola,* a genus of 60 to 70 species of Central and South America. The species employed have only recently been identified (Schultes 1979a, 1979b) as *V. calophylla* Warb. and *V. calophylloidea* Markgr. in Colombia and *V. theiodora* (Spr. ex Benth.) Warb. and *V. elongata* (Spr. ex Benth.) Warb. in Brazil (Carias-Brewer and Steyermark 1976; Maia and Rodrigues 1974b,c; Schultes 1954; Schultes et al. 1969; Schultes and Holmstedt 1968; Seitz 1967). The most intense use of this snuff, called *yakee; paricá, epena,* and *nyakwana,* centers among the Waikas of Brazil and Venezuela. In Colombia, only witch

doctors employ it; but in Brazil the intoxicant is taken by all adult males in excess, either individually at any time or ritually at endocannibalistic ceremonies amongst the Waikas. The resin, which is boiled, dried, pulverized, and occasionally mixed with powdered leaves of a *Justicia* species and bark-ashes of *Theobroma subincanum* Mart. or *Elizabetha princeps* Schomb. ex Benth., acts rapidly and violently. Effects include excitement, numbness of the limbs, twitching of facial muscles, nausea, hallucinations, and finally a deep sleep; use is frequent and it enters into Waika beliefs about the spirits resident in the drug.

Contemporary investigations indicate that the snuff prepared from *Virola theiodora* contains normally up to 8% 5-methoxy-N,N-dimethyltryptamine, with lesser amounts of N,N-dimethyltryptamine (Agurell et al. 1968b; Holmstedt 1965). There is appreciable variation in alkaloid concentration in different parts (leaves, bark, root) of *V. theiodora,* but the content in the bark resin may reach as high as 11%. Two new β-carbolines have likewise been found in *V. theiodora* (Agurell et al. 1968b).

Of other species of *Virola* investigated, *V. rufula* (Mart. ex A.DC.) Warb. contains substantial amounts of tryptamines and *V. calophylla,* one of the species employed in the preparation of snuff in Colombia, contains high amounts of alkaloids, apparently in the leaves alone. *V. multinervia* Ducke and *V. venosa* (Benth.) Warb. are almost devoid of alkaloids (Agurell et al. 1968b). Recently, a number of hallucinogenic substituted tryptamines have been isolated from *V. peruviana* (A.DC.) Warburg, a suspected South American hallucinogenic plant (Lai et al. 1973).

The Witotos, Boras, and Muinanes of Amazonian Colombia utilize the resin of a *Virola,* now identified as *V. theiodora,* orally as an hallucinogen (Schultes 1969e; Schultes and Swain 1976). Small pellets of the boiled resin are rolled in a "salt" left following evaporation of the filtrate of bark ashes of *Gustavia Poeppigiana* Berg ex Mart. and other plants and ingested to bring on a rapid intoxication, during which the witch doctors see and speak with "the little people". There are suggestions that Venezuelan Indians may smoke *V. sebifera* Aubl. as an intoxicant (Schultes 1969e).

Rubiaceae

Psychotria L.

Among the sundry admixtures employed to "strengthen" and "lengthen" the effects of the hallucinogenic drink prepared from *Banisteriopsis Caapi* (Spr. ex Griseb.) Morton and *B. inebrians* Morton in the western Amazon, one of the most commonly added is the leaves of *Psychotria* (Schultes 1967). One species used in Ecuador and Peru, *P. viridis* (Schultes 1966a, 1970c), has recently been shown to contain N,N,-dimethyltryptamine (Rivier and Lindgren 1972). The same species, and another not yet definitely identified, are similarly used in the Acre Territory, Brazil (Prance 1972). Tryptamines have apparently not hitherto been reported from the Rubiaceae.

The genus *Psychotria* comprises more than 700 species from the warmer parts of both hemispheres, many of which have important roles in folk medicine or are poisons.

HALLUCINOGENS OF UNCERTAIN USE OR CHEMICAL COMPOSITION

Sundry plants known to possess psychoactive constituents may be employed as hallucinogens, but corroboratory evidence is necessary. Others are known to be used for their psychotomimetic properties, but the chemical principles responsible for the effects are of uncertain or undetermined structure.

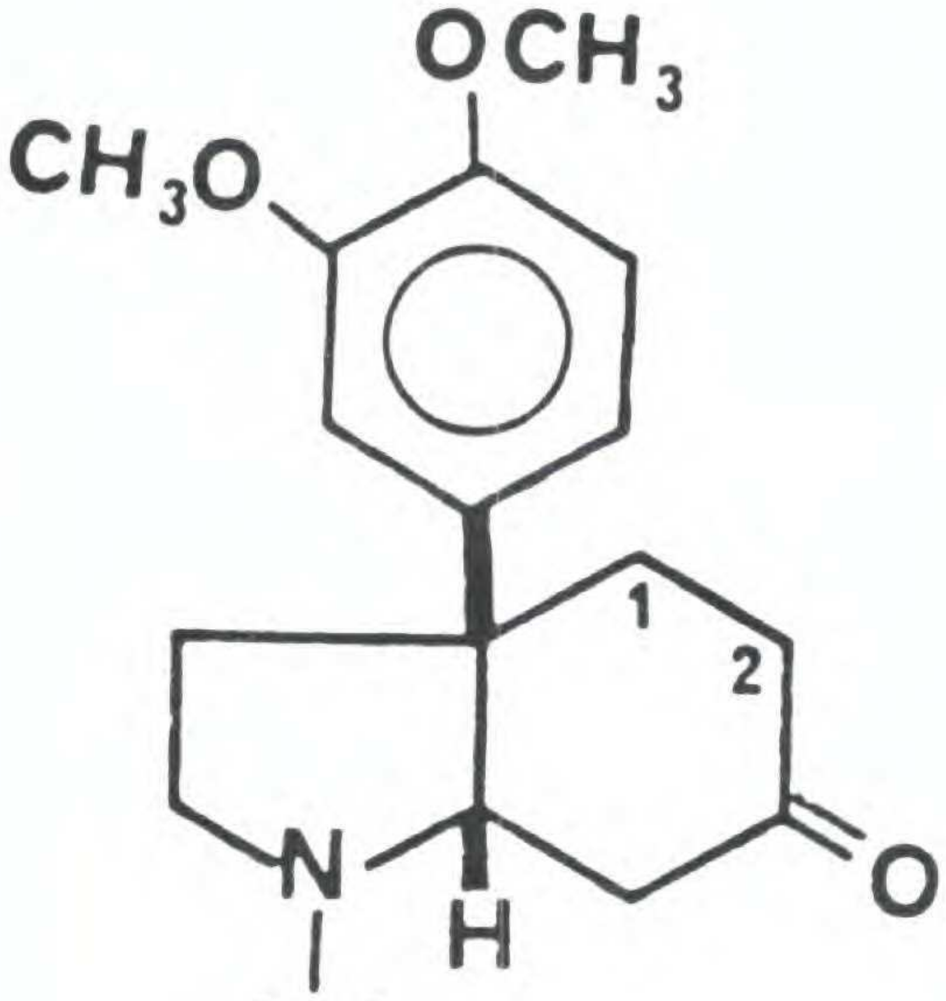
Aizoaceae

Mesembryanthemum L.

More than 225 years ago, the Hottentots of South Africa were reported using a narcotic called *kanna* or *channa.* At the present time, this name applies to sundry species of *Mesembryanthemum (Sceletium),* but especially to *M. tortuosum* L. There is no recent evidence, however, that these are hallucinogenically employed. Other plants—*Sclerocarya Caffra* Sond. of the Anacardiaceae and *Cannabis*—have been suggested as possible identifications (Lewin 1927; Schultes 1967; Schultes and Hofmann 1979).

Several species of *Mesembryanthemum* known to cause a state of stupour when ingested have yielded alkaloids: mesembrine (XXXI) and mesembrenine (XXXII). Both have the

crinane-type characteristic of many amaryllidaceous alkaloids, but differ in having an open ring (Popelak and Lettenbauer 1967). There are about 1000 species of *Mesembryanthemum, sensu lato,* in the xerophytic regions of South Africa. About two dozen species have been split off into a group often recognized as a distinct genus, *Sceletium.*



XXXI

XXXII $\Delta^{1.2}$

Amaryllidaceae

Pancratium L.

The Bushmen of Dobe, Botswana, consider *Pancratium trianthum* Herbert, a bulbous perennial known locally as *kwashi,* to be psychoactive (Schultes 1970a). Rubbing the bulb over incisions on the head is said to induce visual hallucinations. Nothing is known of any possible psychotomimetic constituents, although toxic alkaloids of the tazettine type are characteristic of the genus (Amico et al. 1972). Some of the 15 species of *Pancratium,* mainly Asiatic and African, possess toxic principles, chiefly alkaloids. Some species are employed in folk medicine; others are potent cardiac poisons.

Apocynaceae

Prestonia R. Br.

The source of the hallucinogenic *yajé* of the western Amazon has been reported as *Prestonia (Haemadictyon) amazonica* (Benth.) Macbride an identification allegedly based on misinterpretation of field data and guesswork (Reinburg 1921). Although this assumption is well established in the botanical and chemical literature, recent evaluation of the evidence seriously discredits this suggestion (Schultes and Raffauf 1960). A report of N,N-dimethyltryptamine in *P. amazonica* (Hochstein and Paradies 1957) was based on an erroneous identification, without voucher specimens, of an aqueous extract of the leaves of a vine which may well have been *Diplopterys Cabrerana (Banisteriopsis Rusbyana).*

Cactaceae

Ariocarpus Scheidw.

The Tarahumara Indians of northern Mexico employ *Ariocarpus fissuratus* (Engelm.) K. Schum., called *sunamí hikuri* or *cimarrón,* as a narcotic, asserting that it is stronger than true peyote (*Lophophora*) (Schultes 1967, 1970a).

There are five species known in this genus, all Mexican (Agurell 1969; Der Marderosian 1967a).

Epithelantha Weber ex Britt. & Rose

The Tarahumara likewise use *Epithelantha micromeris* (Engelm.) Weber ex Britt. & Rose as a narcotic (Bye 1979; Schultes 1970c). Chemical studies apparently have not been carried out on representatives of this genus of three species of southwestern United States and Mexico.

Pachycereus (A. Berger) Britt. & Rose

Another cactus utilized as a narcotic by the Tarahumara is the gigantic *Pachycereus pecten-aboriginum* (Engelm.) Britt. & Rose, which they call *cawé* (Bye 1979). Carnegine has been reported from this species (Agurell 1969). Another species, *P. marginatus* (DC.) Britt. & Rose, is said to contain pilocereine (Agurell 1969).

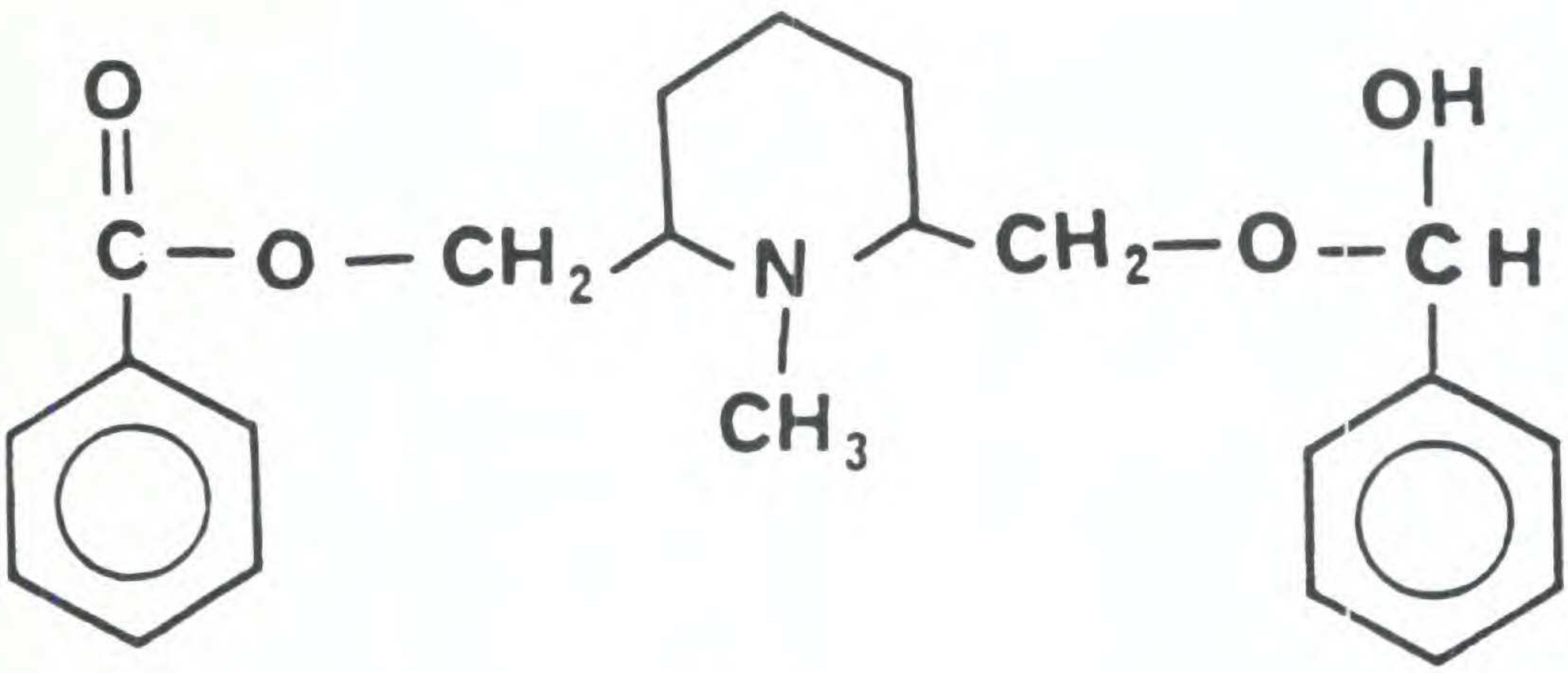
There are five species of *Pachycereus,* all native to Mexico.

Campanulaceae

Lobelia L.

Lobelia Tupa L., a tall polymorphic herb of the Andean highlands known as *tupa* or *tabaco del diablo,* is a widely recognized poison. Chilean peasants are said to employ the juice to relieve toothache, and, while the Mapuches of Chile reputedly smoke the leaves for their narcotic effect, there is as yet no certainty that this plant is truly hallucinogenic (Naranjo 1969).

The leaves of *Lobelia Tupa* contain the piperidine alkaloid lobeline (XXXIII), a respiratory stimulant, and the diketo- and dihydroxy-derivatives, lobelamidine and norlobelamidine (Kaczmarek and Steinegger 1958, 1959).



XXXIII

There are 350 to 400 cosmopolitan species of *Lobelia,* mostly tropical and subtropical, especially in the Americas. It is usually classified with several other large genera as a subfamily, Lobeliodieae, of the Campanulaceae, but the subfamily may sometimes be treated as a distinct family, Lobeliaceae.

Compositae

Calea L.

A common Mexican shrub, *Calea Zacatechichi* Schlechten., belonging to a tropical American genus of about 100 species, represents one of the most recently reported hallucinogens. The Chontal Indians of Oaxaca take the leaves as an infusion for

divination, calling them *thle-pela-kano* or "leaf of god" and believing them to clarify the senses (MacDougall 1960b). Although the plant has long been used in folk medicine (Díaz 1979), chemical studies have revealed only a large number of polyacetylenes, sesquiterpene lactones, chromenes, triterpenes and flavonoids (Bohlmann and Zdero 1977; Quijano, et al. 1977, 1978, 1979), none of which could be expected to account for hallucinogenic effects. Preliminary investigations have indicated the presence of a possible new alkaloid (Holmstedt, pers. commun.).

Coriariaceae

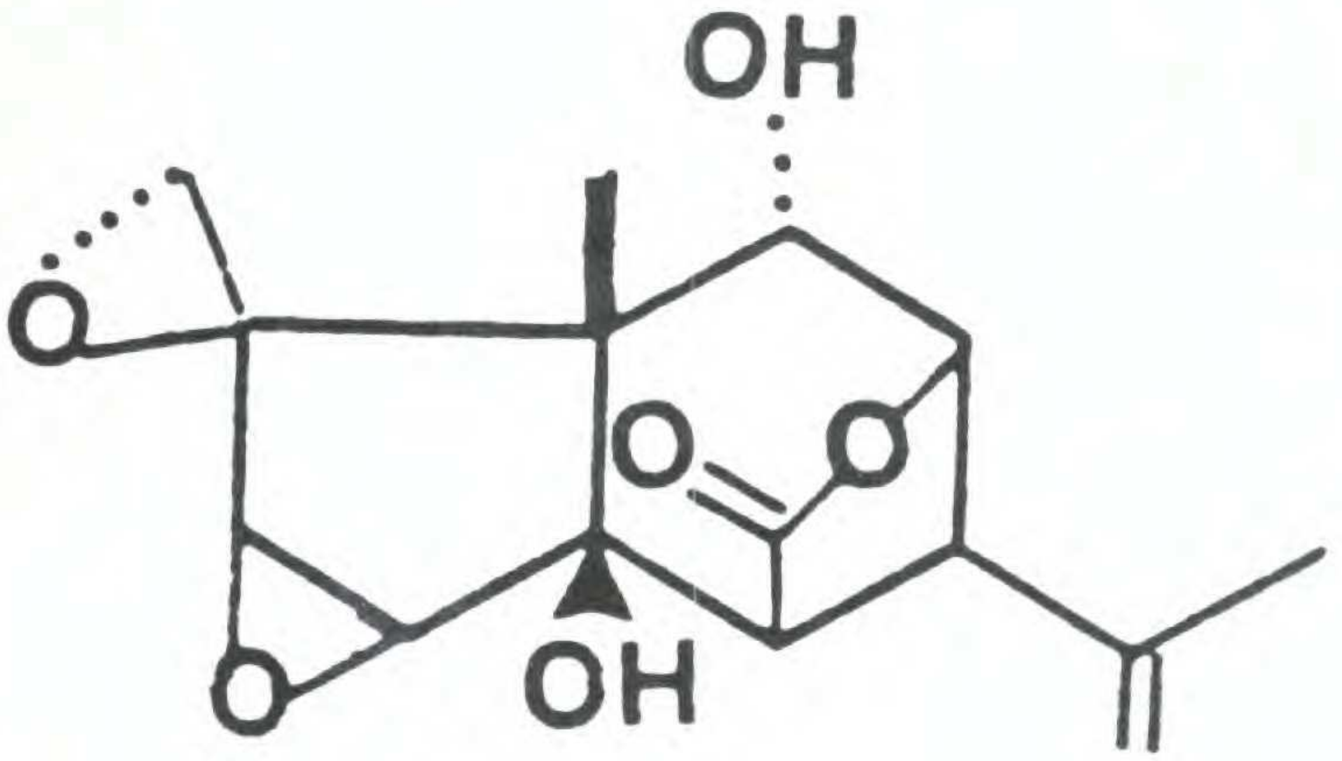
Coriaria L.

Long recognized in the Andes as dangerously toxic to animals, *Coriaria thymifolia* H. & B. ex Willd. has recently been reported as hallucinogenic, giving a sensation of flight. The fruits, reputedly containing catechol derivatives, are eaten for inebriation in Ecuador, where the plant is called *shanshi* (Naranjo, 1969; Naranjo and Naranjo, 1961).

Several toxic and structurally related sesquiterpenes have been isolated from the Coriariaceae: coriaric acid, coriamyrtin, coriatin, tutin (XXXIV), and pseudotutin (Kariyone and Ohsumi 1943; Kinoshita 1929, and 1930; Lowe and White 1972; Maranon, 1932).

Species of *Coriaria* have long been known as toxic plants, and this toxicity could be related to the alleged hallucinogenic activity of *C. thymifolia* (Chelvers 1972).

The genus, the only one in the family, has some 15 species distributed in Eurasia, New Zealand, and highland tropical America.



XXXIV

Desfontainiaceae

Desfontainia R. & P.

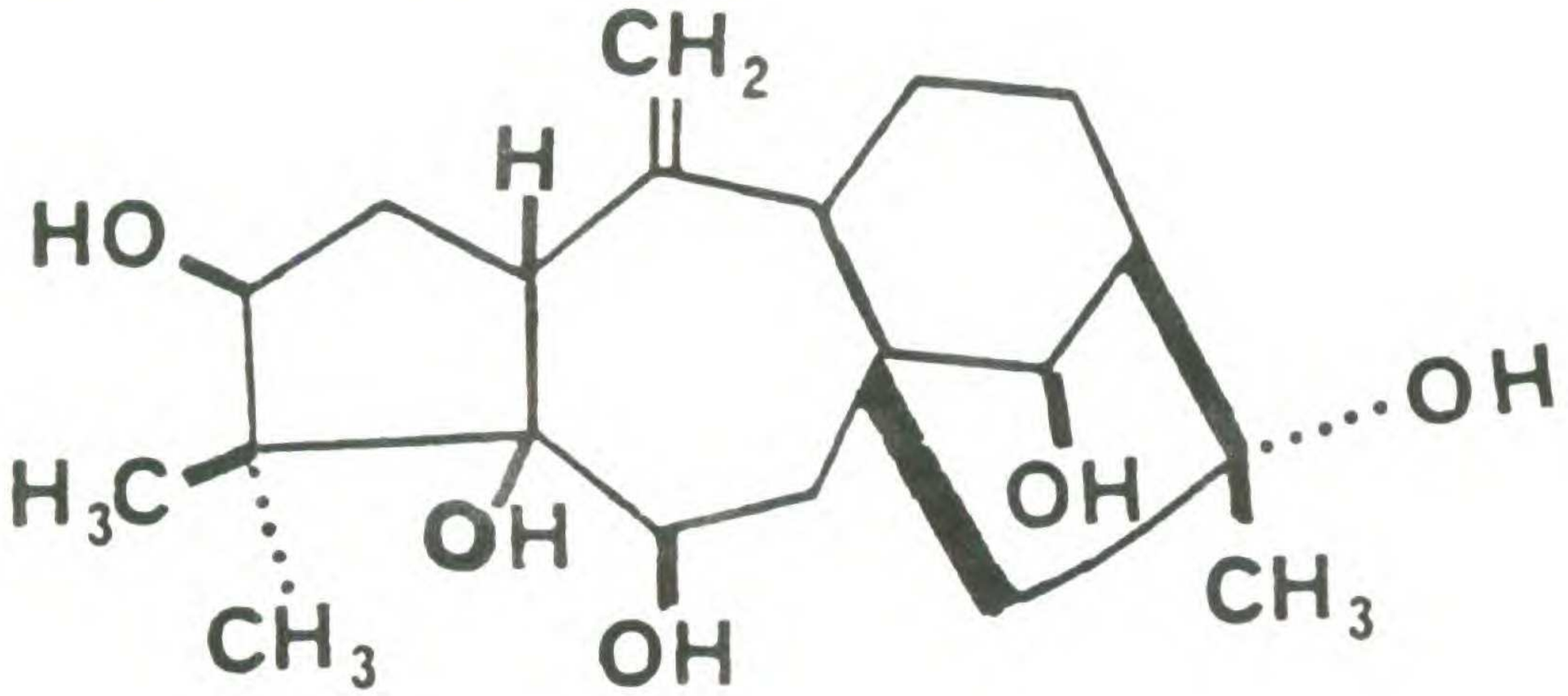
It is reported that the leaves of *Desfontainia spinosa* R. & P. are employed in southern Chile as a narcotic and medicinally (Schultes 1970c). The narcotic use of this plant has now been substantiated in Colombia (Schultes 1977a). Chemical investigation of this anomalous plant have apparently not been carried out. The genus, with some five Andean species, comprises a family which appears to be related to the Loganiacae and which is sometimes placed in the Potaliaceae.

Ericaceae

Pernettya Gaudich.

Pernettya furiens (Hook. ex DC.) Klotsch., known in Chile as *huedhued* or *hierba loca,* is toxic. When consumed in quantity, the fruits induce mental confusion and madness or permanent insanity and exercise a narcotic effect similar to that of *Datura* (Schultes 1970c). This species has apparently not been chemically investigated. Its activity may be due to grayanotoxin III (andromedotoxin) (XXXV), a poisonous principle widely distributed in the family. *Pernettya parvifolia* Benth., called *taglii* in Ecuador, is noted as a toxic plant containing grayanotoxin III and the fruit of which, when ingested, causes hallucinations and other psychic and motor alterations (Chen and Chen 1939; Naranjo 1969).

Some 25 species of *Pernettya* are known from Tasmania, New Zealand, the highlands from Mexico to Chile, the Galapagos and the Falkland Islands.



XXXV

Gomortegaceae

Gomortega R. & P.

Gomortega Keule (Mol.) I. M. Johnst., an endemic of Chile, where it has the Mapuche Indian names *keule* or *hualhual,* may once have been employed as a narcotic (Schultes 1970c). Its fruits are intoxicating, especially when fresh, due possibly to an essential oil. There is only this single species in the whole family Gomortegaceae.

Himantandraceae

Galbulimima F. M. Bailey

In Papua, the leaves and bark of *agara, Galbulimima Belgraveana* (F. Muell.) Sprague, are taken with the leaves of a species of *Homalomena* to induce a violent intoxication that progresses into a sleep in which visions and dreams are experienced (Barrau 1958). Several uncharacterized isoquinoline alkaloids have been isolated from this plant, but the specific pharmacology of the constituents is not clear. (Willaman and Schubert 1961).

Two or three species of *Galbulimima* occur in eastern Malaysia and northeastern Australia.

Labiatae

Coleus Lour., *Salvia* L.

In southern Mexico, crushed leaves of *Salvia divinorum* Epling & Ját.-M., known in Oaxaca as *hierba de la Virgen* or *hierba de la Pastora,* are valued by the Mazatec in divinatory rites, when other more potent hallucinogens are unavailable (Wasson 1962). Although investigators have experimentally substantiated the psychotomimetic effects, an active principle remains to be isolated from the plant (Schultes and Hofmann 1973 and 1980; Wasson 1962). It has been suggested that *S. divinorum* represents the hallucinogenic *pipiltzintzintli* of the ancient Aztecs (Wasson 1962).

There are some 700 species of *Salvia* in the temperate and tropical parts of both hemispheres, but no other species seems to have been reported as an hallucinogen.

The leaves of two other mints, *Coleus pumilus* Blanco and *C. Blumei* Benth., both native to southeast Asia, are similarly employed by the Mazatec (Wasson 1962). Chemical studies of these two species, at least on the basis of material growing in southern Mexico, have not been reported, and a psychoactive principle is not known in this genus of some 150 species of the Old World tropics. An uncharacterized alkane, sterol and triterpene (García et al. 1973), and the flavonoids aromadendrin and cyanidin 3,5-di-0-β-D-glucosyl *p*-coumarate (Lamprecht et al. 1975) have been isolated from *C. Blumei,* but they would not be expected to induce marked pharmacological effects. However, diterpene quinones of the coleon Q type have been isolated from other species of *Coleus* and one might expect compounds of this type to give rise to some type of biological effect (Arihara et al. 1975).

Leguminosae

Erythrina L.

The reddish beans of *Erythrina* may have been valued as hallucinogens in Mexico. Resembling seeds of *Sophora secundiflora,* they are frequently sold in modern Mexican herb markets under the name *colorines* (Schultes 1970c). Several species contain indole or isoquinoline derivatives and could be hallucinogenic.

The genus occurs in the tropics and subtropics of both hemispheres and comprises some 100 species.

Rhynchosia Lour.

The ancient Mexicans may have valued several species of *Rhynchosia* as narcotics. Modern Oaxacan Indians refer to the toxic seeds of *R. pyramidalis* (Lam.) Urb. and *R. longeracemosa* Mart. & Gal. by the same name, *piule,* which they also apply to the seeds of hallucinogenic morning glories. The black and red *Rhynchosia* beans, pictured together with mushrooms, have been identified on Aztec paintings, thus suggesting hallucinogenic use (Schultes 1937b, 1965, 1969a). An as yet uncharacterized alkaloid has been isolated from *R. pyramidalis* (Ristic and Thomas 1962).

This genus comprises some 300 species of tropical and subtropical plants, especially of Africa and America.

Lycoperdaceae

Lycoperdon Pers.

Puffballs, *Lycoperdon marginatum* Vitt. and *L. mixtecorum* Heim, have been reported as hallucinogens utilized by the Mixtecs of Oaxaca in Mexico at 6000 feet altitude or higher (Heim et al. 1967). There are more than 100 species of *Lycoperdon,* native mostly to the temperate zone in moss-covered forests.

The Mixtec call *Lycoperdon mixtecorum, gí-i-wa* ("fungus of first quality") and *L. marginatum,* which has a strong odor of excrement, *gí-i-sa-wa* ("fungus of second quality"). These two hallucinogens do not appear to occupy the place as divinatory agents that the mushrooms hold among the neighboring Mazatec. The most active species, *L. mixtecorum,* causes a state of half-sleep one-half hour after ingestion of one or two specimens. Voices and echoes are heard, and voices are said to respond to questions posed to them. The effects of the puffballs differ markedly from those of the hallucinogenic mushrooms: they may not induce visions, although definite auditory hallucinations do accompany the intoxication. There is as yet no phytochemical basis on which to explain the intoxication from these two gastromycetes, but there seems to be every indication that

further studies are warranted (Schultes and Hofmann 1979; Díaz 1979).

A species of *Lycoperdon* is likewise employed by the Tarahumara of Mexico in witchcraft (Bye 1979).

Malpighiaceae

Tetrapteris Cav.

The Makú Indians in the northwesternmost sector of the Brazilian Amazon prepare a narcotic drink from the bark of *Tetrapteris methystica* R. E. Schult. A cold-water infusion with no admixtures has a yellowish hue and induces an intoxication with visual hallucinations very similar to that caused by drinks prepared from species of the related genus *Banisteriopsis* (Schultes 1954a). Another species, *T. mucronata* Cav., has been indicated as a source in Amazonian Colombia of an hallucinogenic preparation (Schultes 1975).

No chemical studies have been made of these species of *Tetrapteris,* but, since the genus is close to *Banisteriopsis,* it is not improbable that β-carbolines are the active constituents.

Tetrapteris comprises some 80 species, distributed from Mexico to tropical South America and in the West Indies.

Moraceae

Helicostylis Tréc.

Takini is the Caribbean Indian name given to species of large trees of the moraceous genus *Helicostylis* found in the Guianas and in the northeastern part of the Brazilian Amazonia. The bark contains a reddish sap which has mildly poisonous and intoxicating properties, and the hallucinations produced by it form part of witch doctor ceremonies of the Indians and bush negroes of Surinam (Stahel 1944; Ostendorf 1962; Kloos 1971). Much difficulty has been encountered in attempts to obtain botanically authenticated material for chemical and biological studies. The tree has been identified as a species of *Piratinera* or *Brosimum* of the Moraceae (Hegnauer 1969) or even of the euphorbiaceous genus *Pausandra* (de Goeje 1943). On one occasion, material was collected from the wrong tree deliberatly by natives, as they did not want to disclose the identity of their sacred *takini* (Buckley et al. 1973). More recently, the trees

utilized in preparing *takini* have been identified as *H. tomentosa* (P. & E.) Rusby and *H. pedunculata* Ben. (Buckley et al. 1973).

One chemical report on some constituents of takini bark has appeared, but the authors indicate uncertainty concerning the botanical classification of their plant material (Bick and Clezy 1958).

Extracts prepared from the inner bark of both of the aforementioned species have now been pharmacologically evaluated and both are reported to elicit central nervous system depressant effects in mice and rats, and certain of the effects are described as similar to those expected with *Cannabis sativa* (Buckley et al. 1973). Because of the close taxonomic relationship of *Helicostylis* to *Cannabis* (which is classified by some botanists in the Moraceae), one might expect similar types of chemical constituents in both genera. Whether or not the effects are due to the presence of cannabinoids remains to be determined.

Maquira Aubl.

An Amazon jungle tree, *Maquira (Olmedioperebea) sclerophylla* (Ducke) C. C. Berg, represents one of the most poorly understood hallucinogens. The fruits reputedly are the source of an intoxicating snuff employed formerly by Indians of the Pariana region of central Amazonia (Schultes 1970c). A study has been reported in which water and ethanol extracts of *Olmedeoperebea (Maquira) calophyllum* (P. & E.) C. C. Berg wood were devoid of *Cannabis*-like activity in several types of animal tests, even at doses 10 times those required for *C. sativa* to demonstrate such effects (Carlini and Gagliardi 1970). These authors indicate that they are continuing their studies with extracts of *M. calophyllum* and *M. sclerophylla* leaves and flowers, but their results have not as yet been published.

Solanaceae

Brunfelsia L.

Only recently has reliable evidence of the narcotic use of *Brunfelsia* come to light, and further field work is needed to establish the extent of this use. Several vernacular names suggest that the intoxicating properties have long been valued (Schultes 1967). *B. grandiflora* D. Don and *B. Chiricaspi* Plowm. are

frequently added to the narcotic drink prepared from *Banisteriopsis* (Plowman 1973). A species described as *B. Tastevinii* Ben. is reputedly utilized by the Kachinaua of the Brazilian Amazon to prepare an hallucinogenic drink, but this report needs confirmation (Schultes 1970c). Preliminary studies have failed to disclose any chemical constituent in the genus which might be hallucinogenic.

Brunfelsia is a tropical American genus of some 25 species, and is somewhat intermediate between the Solanaceae and Scrophulariaceae.

Iochroma Benth.

The occasional use of tea of the leaves and bark of *Iochroma fuchsioides* (HBK.) Miers as an hallucinogen has been established amongst the Kamsá Indians of Sibundoy in southern Colombia. In the "old days", according to shamans, it was used much more frequently, but to-day, because it is highly toxic, its use is restricted.

This shrub is known as *flor de quinde* ("hummingbird flower"), *nacadero, paguanda* and, in Kamsá, *totubjansuch.* It is also occasionally referred to as *borrachero,* a common name for many intoxicants (Schultes 1977b).

Chemical studies have not yet been carried out on any species of *Iochroma.*

Petunia L.

Petunia (*shanín* in Ecuador) has been reported as an hallucinogen in South America; it is said to induce feelings of levitation (Haro A. 1971).

Interest in Petunia as a possible hallucinogen appears now to be unwarranted, based on an erroneous literature report which it has not been possible to substantiate. Preliminary investigations show no alkaloids with Dragendorff's reagent (Butler, Robinson and Schultes 1981).

Sapindaceae

Ungnadia Endl.

Archeological findings suggest that *Ungnadia speciosa* Endl. seeds may once have been employed as an hallucinogen in Mexico and the Trans-Pecos, Texas (Adovasio and Fry 1976).

The seeds of this tree—*Texas buckeye*—are considered toxic, but as yet no hallucinogenic principles have been reported from the species.

Zingiberaceae

Kaempferia L.

Vague reports indicate that in New Guinea *Kaempferia Galanga* L., known as *maraba,* is employed as an hallucinogen (Schultes 1970c), but phytochemical corroboration is lacking. The rhizome of *K. Galanga,* containing essential oils, is highly prized as a condiment and medicine in tropical Asia.

There are some 70 species of *Kaempferia* distributed in tropical Africa, India to southern China, and western Malaysia.

SUMMARY

This review has attempted to survey those higher plants and fungi recorded in the literature as having been used by primitive or modern peoples as hallucinogens. The ethnomedical history for each, where known, has been summarized, and the active principles, when known, have been identified. The active principles can be broadly classified into a small group of non-nitrogenous compounds and a larger group of nitrogenous substances. In the latter group, the active principles can be classified into eight major skeletons or ring systems, with the indole nucleus being predominant.

A number of minor plants alleged to have been used for hallucinatory purposes at one time or another have been listed in Table 1 for completeness, and a comprehensive bibliography has been provided for the reader having more than a peripheral interest in the subject matter. The bibliography is not exhaustive, however, due to space restrictions.

More than 200 species of higher plants are represented in the survey. That they are widely distributed in the Plant Kingdom is demonstrated by the fact that they belong in 146 genera of more than 50 families. It is truly amazing that of these more than 200 species of hallucinogenic plants, the active principles are known for only about 45. Perhaps the major deterrents for more accelerated studies in this field are two: 1) the lack of a good

Table 1.—Additional Plants Alleged to Have Hallucinogenic Properties[a]

Family	Genus and Species
Aizoaceae	*Mesembryanthemum expansum* L.
	Mesembryanthemum tortuosum L.
Amaranthaceae	*Alternanthera* sp.
	Iresine sp.
Amaryllidaceae	*Ungernia minor*
Apocynaceae	*Haemadictyon* sp.
	Malouetia Tamaquarina A. DC.
	Vinca minor L.
	Voacanga Dregei E. Mey
Araceae	*Arisaema Draconium* Schott
	Panax Schinseng Nees
Anacardiaceae	*Sclerocarya Caffra* Sond.
	Sclerocarya Schweinfurthiana Schinz.
Bignoniaceae	*Tanaecium nocturnum* (Barb.-Rodr.) Bur. & K. Schum.
Boletaceae	*Boletus manicus* Heim
	Heimiella anguiformis Heim
Boraginaceae	*Borago officinalis* L.
Burseraceae	*Boswellia serrata* Roxb.
Cactaceae	*Astrophytum* sp.
	Aztekium sp.
	Carnegiea gigantea (Engelm.) Britt. & Rose
	Cereus peruvianus (L.) Mill.
	Coryphantha compacta (Engelm.) Britt. & Rose
	Dolichothele sp.
	Echinocereus triglochidiatus Engelm.
	Epiphyllum sp.
	Mammillaria Craigii G. Lindsay
	Mammillaria Grahamii Engelm.
	Mammillaria senilis Lodd. ex Scheer
	Neoraimonida macrostibas (Schum.) Britton & Rose
	Obregonia sp.
	Solisia sp.
Campanulaceae	*Lobelia inflata* L.
Cannabaceae	*Humulus Lupulus* L.
Compositae	*Artemisia Absinthium* L.
	Cacalia cordifolia L. fil.
	Cineraria aspera Thunb.
	Helichrysum foetidum (L.) Moench
	Lactuca virosa L.

[a]For original references see Farnsworth, 1972, 1974.

Table 1. *(continued)*

Family	Genus and Species
	Matricaria Chamomilla L.
	Senecio sp.
	Tagetes lucida Cav.
Convolvulaceae	*Ipomoea argyrophylla* Vatke
	Ipomoea Batatas L.
	Ipomoea hederacea Jacq.
	Ipomoea muricata Jacq.
	Stictocardia tiliaefolia (Choisy) Hall. f.
Coprinaceae	*Copelandia cyanescens* (Berk. & Br.) Singer
Cucurbitaceae	*Echinocystis lobata* Torr. & Gray
Cycadaceae	*Dioon edule* Lindl.
Cyperaceae	*Scirpus* sp.
Equisetaceae	*Equisetum arvense* L.
Ericaceae	*Gaultheria* sp.
Euphorbiaceae	*Monadenium Lugardae* N.E. Br.
	Sebastiania Pavoniana Muell.-Arg.
Gnetaceae	*Ephedra nevadensis* Wats.
Gramineae	*Cymbopogon densiflorus* Stapf
	Lagochilus inebrians Bunge
Labiatae	*Leonotis Leonurus Ait. f.*
	Nepeta Cataria L.
	Ocimum micranthum Willd.
Lauraceae	*Cinnamomum Camphora* (L.) T. Nees & Eberm.
Leguminosae	*Astragallus Besseyi* Rdb.
	Astragallus amphioxys A. Gray
	Astragallus molissimus Torr.
	Caesalpinia sepiaria Roxb.
	Canavalia maritimia Petit-Thouars
	Erythrina americana Mill.
	Mimosa verrucosa Benth.
	Mucuna pruriens (L.) DC.
	Rhynchosia phaseoloides DC.
	Swainsonia galegifolia R.Br.
	Zornia latifolia DC.
Loganiaceae	*Gelsemium sempervirens* Ait.
Loranthaceae	*Phrygilanthus eugenioides* (L.) HBK.
Lythraceae	*Heimia myrtifolia* Hort. Berol. ex. Cham. & Schlecht.
Malpighiaceae	*Banisteriopsis quitensis* (Ndz.) Morton
	Mascagnia psilophylla (Juss.) Griseb. var. *antifebrilis* (R. & P.) Ndz.
Menispermaceae	*Cocculus Leaeba* DC.
Musaceae	*Musa sapientum* L.
Myristicaceae	*Virola cuspidata* (Benth.) Warb.

Table 1. *(continued)*

Family	Genus and Species
Nyctaginaceae	*Mirabilis multiflora* A. Gray
Nymphaeaceae	*Nymphaea ampla* (Salisb.) DC.
	Nymphaea caerulea Sav.
Orchidaceae	*Oncidium Cebolleta* (Jacq.) Sw.
Palmae	*Areca Catechu* L.
Pandanaceae	*Pandanus* sp.
Papaveraceae	*Argemone mexicana* L.
	Eschscholzia californica Cham.
	Papaver somniferum L.
Passifloraceae	*Passiflora incarnata* L.
Phytolaccaceae	*Phytolacca acinosa* Roxb.
Piperaceae	*Piper Betle* L.
	Piper methysticum Forst.
	Piper nigrum L.
Ranunculaceae	*Ranunculus acris* L.
Rubiaceae	*Corynanthe Johimbe* K. Schum.
	Mitragyna speciosa Korth
Russulaceae	*Russula* spp.
Rutaceae	*Evodia Bonwickii* F. v. Muell
Sapindaceae	*Paullinia Yoco* R.E. Schult. & Killip
	Nephelium Topengii (Merr.) H.S Lo
Saxifragacea	*Hydrangea paniculata* Sieb.
Scrophulariaceae	*Digitalis purpurea* L.
Solanaceae	*Capsicum frutescens* L. var. *grossum* (L.) Bailey
	Cestrum laevigatum Schlecht.
	Datura fastuosa L.
	Duboisia Hopwoodii F. v. Muell.
	Hyoscyamus albus L.
	Hyoscyamus muticus L.
	Nicotiana rustica L.
	Nicotiana Tabacum L.
Styracaceae	*Styrax Tessmannii* Perk.
Turneraceae	*Turnera diffusa* Willd. ex Schult.
Umbelliferae	*Daucus Carota* L.
	Ferula Sumbul Hook. f.
	Foeniculum vulgare Mill.
	Peucedanum japonicum Thunb.
	Siler divaricatum Benth. & Hook. f.
Valerianaceae	*Valeriana officinalis* L.
Zingiberaceae	*Zingiber officinale* Rosc.

animal model which the interested chemist would find necessary in monitoring his isolation work; and 2) the sparsity of field work of a scientific nature in the fast disappearing aboriginal societies. Further ethnobotanical field work will surely lead to the discovery of additional hallucinogenic plants and to more information on those already known.

The Plant Kingdom remains a fertile and almost virgin territory for those interested in the discovery of new psychoactive drugs, not to mention other types of biologically active compounds waiting in silent hiding. Can we afford to neglect any longer the hunting ground that until now has provided, mainly through folklore and serendipity, leads that the pharmaceutical industry has turned into products having annual sales in excess of $3,000,000,000 in the American prescription market alone? (Farnsworth and Morris 1976).

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